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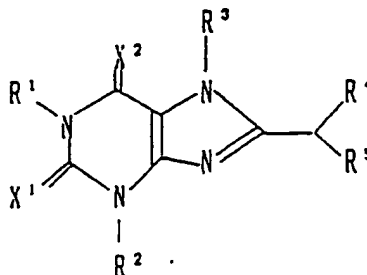
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54 **Xanthine derivatives.**

57 Novel xanthine compounds represented by the following formula:



and pharmaceutically acceptable salts thereof have a diuretic action, a renal-protecting action and a vasodilative action.

The compounds are useful as a diuretic, a renal-protecting agent and an antihypertensive agent.

## XANTHINE DERIVATIVES

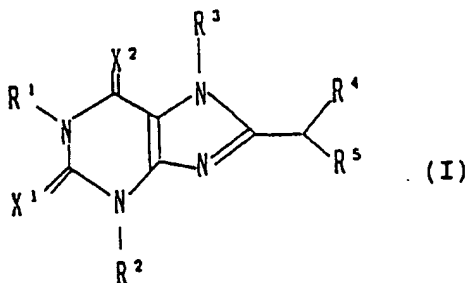
The present invention relates to novel xanthine derivatives having diuretic action, renal-protecting action and vasodilative action.

Heretofore, theophylline, i.e., 1,3-dimethylxanthine has been known as a diuretic, a vasodilator, etc. [The Merck Index, 10th edition, 9114 (1983)].

Theophylline analogues represented by the following general formula (I) wherein both R<sup>4</sup> and R<sup>5</sup> are alkyl have a diuretic action, as disclosed in East German Patent No. 31,772 [Chem. Abst., 63, 18120d (1965)] (CA-724,173A); J. Am. Chem. Soc., 75, 114 (1953) and J. Med. Chem., 14, 1202 (1971), and also have a bronchodilative action, as disclosed in JP-A- 166191/81 (US-A-4,546,182), JP-A-163381/82 (GB-A-2091249) and JP-A-41478/88 (EP-A-256692). Furthermore xanthine derivatives having an anti-inflammatory action and other activities are disclosed in JP-A-66583/80 (US-A-4,299,832); Japanese National Publication of translated version No. 500666/86 (US-A-4,558,051); US-A- 3,624,215 and 3,624,216.

The present invention provides novel xanthine derivatives represented by the formula (I) wherein R<sup>4</sup> and R<sup>5</sup> are alicyclic alkyl or aryl groups and having diuretic action, renal-protecting action, vasodilative action, etc.

The present invention relates to xanthine derivatives represented by the following general formula (I):



wherein each of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> independently represents hydrogen or lower alkyl; each of R<sup>4</sup> and R<sup>5</sup> independently represents substituted or unsubstituted alicyclic alkyl, or substituted or unsubstituted aryl; and each of X<sup>1</sup> and X<sup>2</sup> independently represents oxygen or sulfur [hereinafter referred to as "Compound (I)" and compounds with other formula numbers are likewise referred to], or pharmaceutically acceptable salts thereof.

In the definition of the respective groups in the formula (I), the lower alkyl includes straight or branched alkyl having 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, etc. The alicyclic alkyl includes those having 3 to 8 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, etc. The aryl includes phenyl, naphthyl, etc. The substituent on the alicyclic alkyl and aryl independently includes lower alkyl, hydroxy, lower alkoxy, halogen, amino, nitro, etc., and the number of the substituents is 1 to 3. As the lower alkyl and the alkyl moiety in the lower alkoxy, mention may be made of the same groups as defined in the aforementioned lower alkyl. The halogen includes fluorine, chlorine, bromine and iodine.

The pharmaceutically acceptable salts of Compound (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, amino acid addition salts, etc.

The pharmaceutically acceptable acid addition salts of Compound (I) include inorganic acid salts such as hydrochlorides, sulfates, phosphates, etc., and organic acid salts such as acetates, maleates, fumarates, oxalates, citrates, etc.

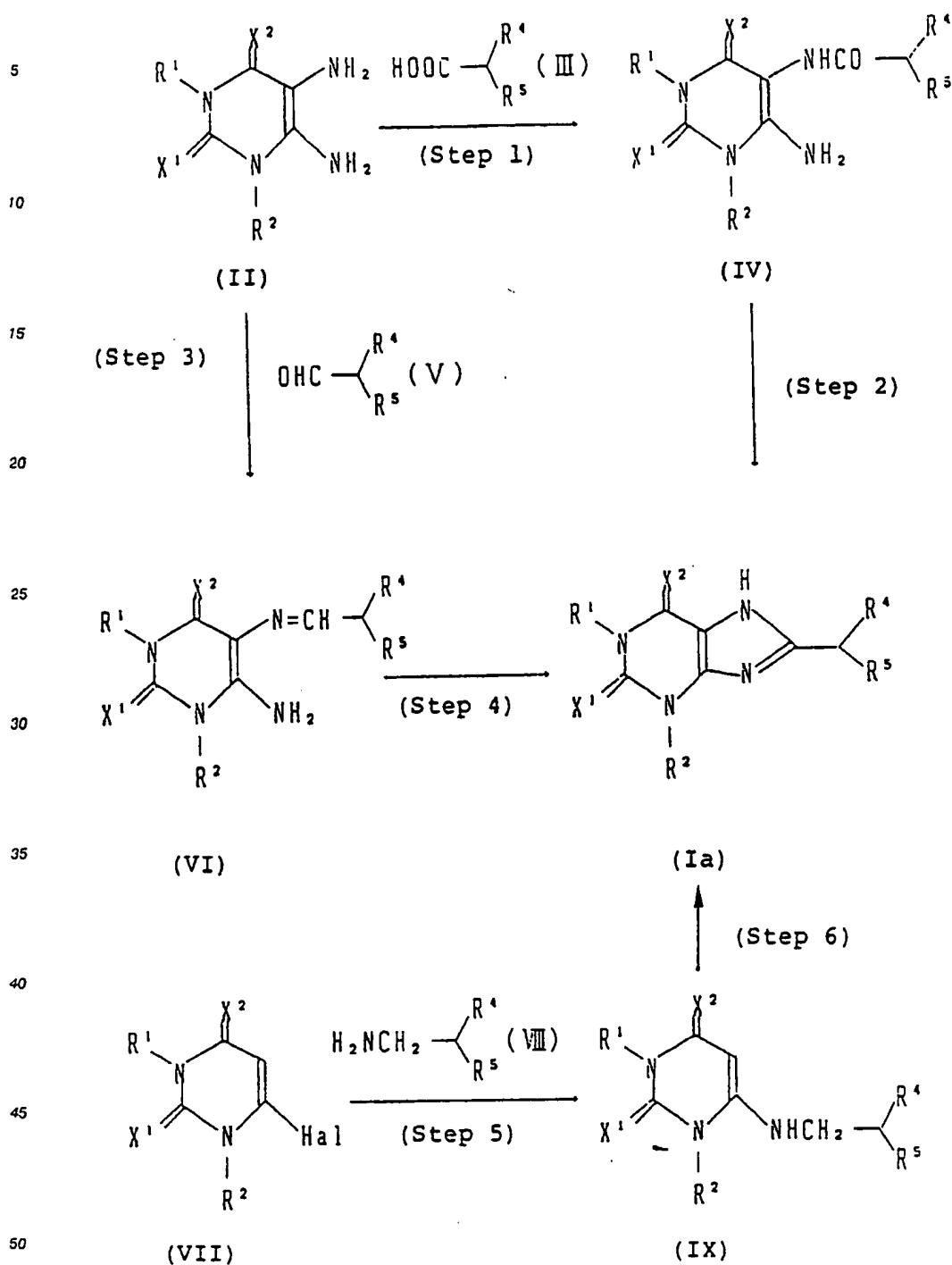
The pharmaceutically acceptable metal salts include alkali metal salts such as sodium salts, potassium salts, etc., alkaline earth metal salts such as magnesium salts, calcium salts etc., and also aluminum and zinc salts.

The ammonium salts include salts of ammonium, tetramethylammonium, etc. The pharmaceutically acceptable organic amine addition salts include addition salts of morpholine, piperidine, etc., and the pharmaceutically acceptable amino acid addition salts include addition salts of lysine, glycine, phenylalanine, etc.

A process for producing the compounds of the present invention will be described below.

Compound (Ia) which is Compound (I) wherein R<sup>3</sup> is hydrogen, can be produced by the following

production steps:



wherein Hal represents halogen such as chlorine, bromine or iodine and R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, X<sup>1</sup> and X<sup>2</sup> have the same meanings as defined above.

Step 1:

A Compound (IV) can be obtained by reacting a uracil derivative (II) obtained according to a well known process [for example, the process disclosed in JP-A- 42383/84] with carboxylic acid (III) or a carboxylic acid reactive derivative.

The carboxylic acid reactive derivative includes acid halides such as acid chlorides, acid bromides, etc., active esters such as p-nitrophenyl ester, N-oxy succinimide ester, etc., acid anhydrides commercially available or those formed from carbodiimides such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diisopropylcarbodiimide, dicyclohexylcarbodiimide, etc.; mixed acid anhydrides with monoethyl carbonate, monoisobutyl carbonate, etc. and so forth.

The reaction of Compound (II) with Compound (III) can be carried out without any solvent at a temperature of 50 to 200 °C. In the case of using the carboxylic acid reactive derivative, the reaction can be carried out according to a process usually used in the peptide chemistry. For example, the reaction solvent is properly selected from halogenohydrocarbons such as methylene chloride, chloroform, dichloroethane, etc., ethers such as dioxane, tetrahydrofuran, etc., dimethylformamide and dimethylsulfoxide, and if necessary water is used. The reaction temperature is -80 to 50 °C, and the reaction is completed for 0.5 to 24 hours. Sometimes, the reaction may be favorably carried out, if necessary, in the presence of an additive such as 1-hydroxybenzotriazole, etc., or a base such as pyridine, triethylamine, dimethylaminopyridine, N-methylmorpholine, etc. Furthermore, the carboxylic acid reactive derivative may be formed in the reaction system and used without isolation.

#### Step 2:

A desired Compound (Ia) with a closed ring can be obtained from Compound (IV) by the reaction in the presence of a base (process A), by treatment with a dehydrating agent (process B), or by heating (process C).

As the preferable base in the process A, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, etc. can be exemplified. As the reaction solvent, water, lower alcohols such as methanol, ethanol, etc., ethers such as dioxane, tetrahydrofuran, etc., dimethylformamide, dimethylsulfoxide, etc. can be used alone or in combination. The reaction is carried out at a temperature of from room temperature to 180 °C and is usually completed for 10 minutes to 6 hours.

As the dehydrating agent for use in the process B, thionyl halides such as thionyl chloride, etc., and phosphorus oxyhalides such as phosphorus oxychloride, etc. can be used, and the reaction is carried out at a temperature of from room temperature to 180 °C without any solvent or in a solvent inert to the reaction, for example, halogenohydrocarbons such as methylene chloride, chloroform, dichloroethane, etc., dimethylformamide, dimethylsulfoxide, etc. and is usually completed for 0.5 to 12 hours.

In the case of process C, the Compound (Ia) can be obtained by heating Compound (IV) at a temperature of 50 to 200 °C in a polar solvent such as dimethylsulfoxide, dimethylformamide, Dowthermo A (product of Muromachi Kagaku Kogyo Kaisha, Ltd.), etc.

#### Step 3:

A schiff base (VI) can be obtained by reacting Compound (II) with aldehyde (V) in a mixed solvent such as a mixture of acetic acid with a lower alcohol such as methanol, ethanol, etc. at a temperature of -20 to 100 °C.

#### Step 4:

A desired Compound (Ia) can be obtained by subjecting Compound (VI) to an oxidative cyclization reaction.

As the appropriate oxidizing agent, oxygen, ferric chloride, cerium<sup>IV</sup> ammonium nitrate, diethyl azodicarboxylate, etc. can be exemplified. The reaction is carried out by heating Compound (VI) at from room temperature to 180 °C in the presence of the afore-mentioned oxidizing agent and, if necessary, in a solvent inert to the reaction, for example, a lower alcohol such as methanol, ethanol, etc., a halogenohydrocarbon such as methylene chloride, chloroform, etc., or an aromatic hydrocarbon such as toluene, xylene, nitrobenzene, etc.

Step 5:

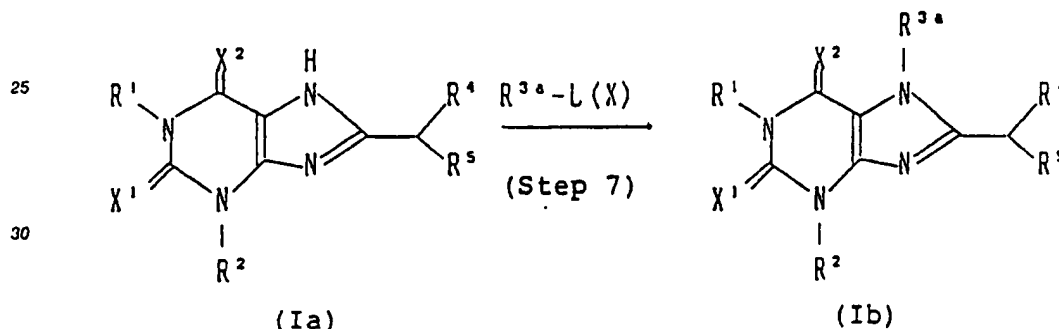
A Compound (IX) can be obtained by reacting a uracil derivative (VII) obtained according to a well known process, for example, the process described in Japanese Published Unexamined Patent Application No. 5082/86 with an amine (VIII) in a solvent inert to the reaction, for example, a lower alcohol such as methanol, ethanol, etc., dimethylformamide, dimethylsulfoxide, etc. alone or in combination thereof at a temperature of 50 of 150 °C.

10 Step 6:

A Compound (Ia) can be obtained by reacting a Compound (IX) with a nitrosating agent such as a nitrite derivative such as sodium nitrite, isoamyl nitrite, etc. under an acidic condition of dilute hydrochloric acid, etc. in a solvent inert to the reaction, for example, a lower alcohol such as methanol, ethanol, etc. usually at a temperature of from room temperature to the boiling point of the solvent.

Step 7:

20 A Compound (Ib) which is Compound (I) wherein R<sup>3</sup> is a lower alkyl group can be obtained through the following step:



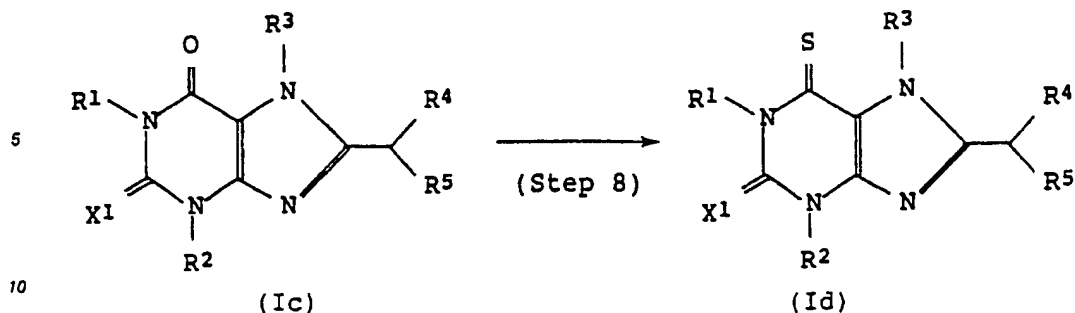
35 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, X<sup>1</sup> and X<sup>2</sup> have the same meanings as defined above, R<sup>3a</sup> represents a lower alkyl in the definition of R<sup>3</sup> and L represents a leaving group.

As the leaving group, halogen such as bromine, iodine, etc., alkylsulfonyloxy such as methanesulfonyloxy, etc., and arylsulfonyloxy such as p-toluenesulfonyloxy, etc. can be exemplified.

40 A desired compound (Ib) can be obtained by reacting Compound (Ia) obtained in Steps 1 to 6 with an alkylating agent (X) preferably in the presence of a base. As the base, an alkali metal carbonate such as sodium carbonate, potassium carbonate, etc., an alkali metal hydride such as sodium hydride, etc., and an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, etc. can be exemplified. The reaction is completed at a temperature of 0 to 180 °C usually for 0.5 to 24 hours.

Step 8:

50 Compound (Id) which is Compound (I) wherein X<sup>2</sup> is sulfur, can be obtained according the following step.



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and X<sup>1</sup> have the same meanings as previously defined.

A desired Compound (Id) was prepared by reacting Compound (Ic) obtained by the above-mentioned steps which is Compound (I) wherein X<sup>2</sup> is oxygen, with an appropriate thionation reagent, in an inert solvent. As the thionation reagent, phosphorus pentasulfide and the like are mentioned. As the solvent, dimethylformamide, tetrahydrofuran, dioxane, etc. are mentioned, and preferably pyridine and the like are used. The reaction is carried out at a temperature of 50 to 180 °C for a period of 10 minutes to 12 hours.

The intermediates and the desired compounds obtained according to the aforementioned processes can be isolated and purified by subjecting them to a purification process usually used in the organic synthetic chemistry, for example, filtration, extraction, washing, drying, concentration, recrystallization, various chromatographies, etc. The intermediates can be used in the successive reaction without any purification.

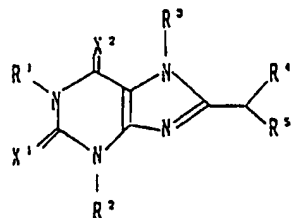
Salts of Compounds (I) can be obtained by direct purification when Compound (I) can be obtained in a salt form, or by formation of a salt according to a usual procedure when the Compound (I) is obtained in a free form, and a subsequent purification.

Compounds (I) and their pharmaceutically acceptable salts sometimes exist in an adduct form with water or various other solvents, and these adducts are included in the present invention.

Optical isomers may exist with respect to Compounds (I), and all the possible stereoisomers and their mixtures are also included in the scope of the present invention.

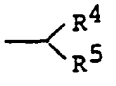




Specific examples of Compounds(I) are shown in Table 1, where compound numbers correspond to Example numbers appearing hereinafter:

Table 1



Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>		X <sup>1</sup>	X <sup>2</sup>
1	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
2	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
3	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
4	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
5	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
6	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
7	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
8	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
9	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		S	O
10	H	n-C <sub>3</sub> H <sub>7</sub>	H		O	O



Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>		X <sup>1</sup>	X <sup>2</sup>
11	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>		O	O
12	H	n-C <sub>3</sub> H <sub>7</sub>	H		O	S
13	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	C <sub>2</sub> H <sub>5</sub>		O	O
14	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>		O	O

Compounds(I) of the present invention and their pharmaceutically acceptable salts have diuretic action, renal-protecting action and vasodilative action and thus Compounds (I) are useful as a diuretic, a renal-protecting agent and an antihypertensive agent.

The pharmacological action of Compounds(I) will be explained, referring to Test Examples.

#### Test Example 1, diuretic action

Wistar rats (male: 150 -300 g) were starved for 18 hours prior to the administration of the test compound. A test compound (25 mg/kg) and saline (25 ml/kg) were orally administered to test rats and only saline was administered to control rats. Three groups, each group consisting of 3 rats, were used for each test compound. Urine was collected 30 for 6 hours after the administration. Urine volume was measured and the electrolytes (Na and K) in the urine were determined with a flame photometer (775A, Hitachi, Ltd., Japan). The results are shown in Table 2.

All parameters are expressed as relative values of control. The compound Nos. 1, 4 and 11 exhibited more potent activity in the urine volume and have much higher ratios of Na to K than the reference compounds.

Table 2

Compound No.	Urine amount	Na <sup>+</sup> excretion	K <sup>+</sup> excretion	Na <sup>+</sup> /K <sup>+</sup>
	(%)	(%)	(%)	
(Control)	100	100	100	1.00
1	244	216	127	1.71
2	102	96	88	1.08
3	128	129	101	1.28
4	198	221	123	1.83
8	124	119	113	1.05
11	280	180	92	1.46
Aminophylline* <sup>1</sup> (Reference compound)	134	189	117	1.62
Furosemide* <sup>2</sup> (Reference compound)	175	164	157	1.05

\*1 The Merck Index, 10th edition, page 476 (1983)

\*2 The Merck Index, 10th edition, page 4189 (1983)

#### Test Example 2, renal-protecting action (glycerol-induced renal failure model).

A renal failure is a state where the renal function is lowered and the stationary state of a body fluid can be no more maintained. It is known that an acute renal failure characteristic of uriniferous tubule disorder is caused by subcutaneous or intramuscular injection of glycerol to rats [Can. J. Physiol. Pharmacol., 65, 42 (1987)].

Wistar rats (male) were kept deprived of water for 18 hours, and served for the test. A test compound was intraperitoneally administered to the rats (dosage: 10 mg/kg) and the rats were anesthetized with ether and 50% glycerol was subcutaneously administered (dosage: 0.8 ml/100g) to the rats, pinching the dorsal skin. Twenty four hours after the administration of glycerol, the rats were anesthetized with ether and 5 ml of blood was collected from the abdominal aorta. The collected blood was allowed to stand for 30 minutes or longer and then centrifuged at 3,000 rpm for 10 minutes, and the serum creatinine was measured by creatinine test Wako (Jaff'e method).

On the other hand, the left kidneys of the blood-sampled rats were removed and placed in formalin-filled vial bottles, and used as samples for the pathological examination.

According to the test results, compounds Nos. 1, 8 and 11 significantly suppressed an increase in the serum creatinine at a dosage of 10 mg/kg [i.p.] (Compound No. 1:  $p < 0.05$ ; Compound No. 8:  $p < 0.001$ ; compound No. 11:  $p < 0.001$ ), whereas aminophylline had no substantial effect of suppressing the increase. On the contrary, furosemide showed a tendency to increase the serum creatinine. The pathological examination of removed kidneys indicates that compounds Nos. 1, 8 and 11 also significantly improved the state of kidneys.

Compounds (I) or their pharmaceutically acceptable salts can be used as such or in various medicament forms. The present pharmaceutical composition can be prepared by uniformly mixing an effective amount of Compound (I) or its pharmaceutically acceptable salts as an active component with a pharmaceutically acceptable carrier. The pharmaceutical composition is desirably in a unit dosage form applicable to oral or injection administration.

In the preparation of pharmaceutical compositions in an oral dosage form, some useful, pharmaceutically acceptable carrier can be used. For example, liquid, orally administerable compositions such as suspension compositions or syrup compositions can be prepared with water, a saccharide such as sucrose, sorbitol, fructose, etc., a glycol such as polyethyleneglycol, propyleneglycol, etc., an oil such as sesame oil, olive oil, soybean oil, etc., an antiseptic such as p-hydroxybenzoic acid esters, etc., and a flavor such as strawberry flavor, peppermint, etc. Powder, pills, capsules and tablets can be prepared with a vehicle such as lactose, glucose, sucrose, mannitol, etc., a disintegrator such as starch, sodium alginate, etc., a lubricant such as magnesium stearate, talc, etc., a binder such as polyvinyl alcohol, hydroxypropyl cellulose, gelatin,

etc., a surfactant such as fatty acid esters, etc., a plasticizer such as glycerin, etc. and so forth. Tablets and capsules are most useful unit for oral administration because of easy administration. In the preparation of tablets or capsules, a solid pharmaceutical carrier is used.

Injection solutions can be prepared with a carrier such as distilled water, saline solution, glucose solution, or a mixture of saline solution and glucose solution.

Effective dosage and number of administration of a Compound (I) or its pharmaceutically acceptable salts depend on the administration route and ages, body weights, symptoms, etc. of patients, and it is preferable to usually administer Compound (I) at a dosage of 1 to 50 mg/kg per day in 3 to 4 divisions.

The present invention will be described below, referring to Examples.

#### Example 1

##### 8-(1,1-Dicyclopropylmethyl)-1,3-dipropylxanthine (Compound No. 1)

At first, 1.40g (10 mmol) of 1,1-dicyclopropylacetic acid was dissolved in 25 ml of pyridine, and 0.78 ml (11 mmols) of thionyl chloride was added thereto. Then, the mixture was stirred at 60 °C for 10 minutes. Then, a solution of 2.26g (10 mmols) of 5,6-diamino-1,3-dipropyluracil in 15 ml of pyridine was added thereto under ice cooling, and the mixture was stirred for one hour. Then, the solvent was concentrated to approximately one-half under reduced pressure and the residue was poured into ice water and subjected to extraction with chloroform three times. The extract was washed with brine, and dried over anhydrous sodium sulfate and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% methanol/chloroform) to afford 2.33g (yield: 67%) of amorphous 6-amino-5-(1,1-dichloropropyl)acetylamino-1,3-dipropyluracil [Compound (IV): R<sup>1</sup> = R<sup>2</sup> = n-C<sub>3</sub>H<sub>7</sub>; R<sup>4</sup> = R<sup>5</sup> = —CH<sub>2</sub>; X<sup>1</sup> = X<sup>2</sup> = O]

NMR (CDCl<sub>3</sub>; 90 MHz) δ (ppm): 7.71 (brs, 1H), 5.52 (brs, 2H), 4.00 - 3.75 (m, 4H), 1.90 - 1.50 (m, 4H), 1.40 - 0.20 (m, 17H)

Then, 10 ml of phosphorus oxychloride was added to the thus obtained compound and the mixture was refluxed for two hours. After concentration under reduced pressure, the residue was poured into ice water and the pH was adjusted to 6.5 with an aqueous 2N sodium hydroxide solution. Then, the mixture was extracted with chloroform three times, and the combined extract was washed with brine and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 30% ethyl acetate/hexane) and recrystallized from ethanol-water to afford 1.33g (yield: 60%) of the captioned Compound No.1 as a white needle crystal.

Melting point: 129.1 - 130.4 °C

Elemental analysis (C <sub>18</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> )	
Calculated (%):	C 65.43, H 7.93, N 16.96
Found (%):	C 65.53, H 8.11, N 16.82

IR (KBr) ν<sub>max</sub> (cm<sup>-1</sup>): 1700, 1654, 1498

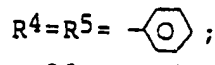
NMR (CDCl<sub>3</sub>; 270 MHz) δ (ppm): 12.70 (brs, 1H), 4.13 (t, 2H), 3.97 (t, 2H), 1.90 - 1.60 (m, 5H), 1.50 - 1.35 (m, 2H), 1.10 - 0.90 (m, 6H), 0.75 - 0.60 (m, 2H), 0.50 - 0.20 (m, 6H)

#### Example 2

##### 8-(1,1-Diphenylmethyl)-1,3-dipropylxanthine (Compound No.2)

At first, 2.00g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil was dissolved in 10 ml of pyridine and 2.45g (10.6 mmol) of diphenylacetyl chloride was added thereto under ice cooling. After stirring for 40 minutes, the mixture was poured into ice water and extracted with toluene three times. The extract was successively washed with water, an aqueous saturated sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford 3.92g of

amorphous 6-amino-5-(1,1-diphenyl)acetyl-amino-1,3-dipropyluracil [Compound (IV):  $R^1 = R^2 = n\text{-C}_3\text{H}_7$ ;



$X^1 = X^2 = \text{O}$ ]

Then, 36 ml of dioxane and 36 ml of an aqueous 2N sodium hydroxide solution were added to 3.62g of the thus obtained compound and the mixture was refluxed under heating for 35 minutes. After cooling, the mixture was neutralized and extracted with chloroform three times. Then, the extract was washed with brine and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, and recrystallized from cyclohexane to afford 2.53g (total yield: 86%) of the captioned Compound No. 2 as a white powder. Melting point: 167.1 - 168.5 °C

Elemental analysis ( $\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_2$ )	
Calculated (%):	C 71.62, H 6.51, N 13.92
Found (%):	C 71.65, H 6.51, N 13.70

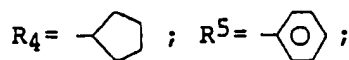
IR (KBr)  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1708, 1649, 1557, 1493

NMR ( $\text{CDCl}_3$ ; 90 MHz)  $\delta$  (ppm): 7.35 - 7.05 (m, 10H), 5.68 (s, 1H), 4.20 - 3.75 (m, 4H), 1.95 - 1.45 (m, 4H), 1.10 - 0.80 (m, 6H)

### Example 3

#### 8-(1-Cyclopentyl-1-phenylmethyl)-1,3-dipropylxanthine (Compound No. 3)

At first, 2.17g (10.62 mmol) of 2-phenylcyclopentane acetic acid and 2.04g (10.62 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride were added to a solution of 2.00g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil in 40 ml of dioxane and 20 ml of water and the mixture was stirred at room temperature for 4 hours while adjusting the pH to 5.5. The pH of the mixture was adjusted to pH 7.5, and then the mixture was extracted with chloroform three times, and the extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 2% methanol/chloroform) to afford 1.73g (yield: 47%) of amorphous 6-amino-5-(1-cyclopentyl-1-phenyl)acetyl-amino-1,3-dipropyluracil [Compound (IV):  $R^1 = R^2 = n\text{-C}_3\text{H}_7$ ;



$X^1 = X^2 = \text{O}$ ]

MS (m/e): 412, 253, 226, 225, 159, 91

NMR ( $\text{CDCl}_3$ ; 90 MHz)  $\delta$  (ppm): 7.50 - 7.00 (m, 5H), 5.22 (brs, 2H), 4.00 - 3.60 (m, 4H), 3.28 (d, 1H,  $J = 11$  Hz), 2.8 - 2.45 (m, 1H), 2.10 - 0.80 (m, 18H)

Then, 13 ml of phosphorus oxychloride was added to 1.28g (3.11 mmol) of the thus obtained compound and the mixture was refluxed under heating for 30 minutes. Then, the mixture was concentrated under reduced pressure and the residue was poured into ice water. The pH was adjusted to 6.5 with an aqueous 2N sodium hydroxide solution. The mixture was extracted with chloroform three times and the extract was washed with brine and dried over anhydrous sodium sulfate. Then, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: 25% ethyl acetate/hexane), and recrystallized from isopropanol-water to afford 730 mg (yield: 59%) of the captioned Compound No. 3 as a white powder. Melting point: 136.6 - 138.1 °C

EP 0 386 675 A2

Elemental analysis (C <sub>23</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub> )	
Calculated (%):	C 70.02, H 7.66, N 14.20
Found (%):	C 69.91, H 7.77, N 14.14

IR (KBr)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 1703, 1654, 1496

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 12.80 (brs, 1H), 7.60 - 7.15 (m, 5H), 4.20 - 4.05 (m, 4H), 3.90 (d, 1H, J=11.0 Hz), 3.10 - 2.90 (m, 1H), 2.00 - 1.50 (m, 10H), 1.30 - 0.90 (m, 8H)

Example 4

8-(1-Cyclopropyl-1-phenylmethyl)-1,3-dipropylxanthine (Compound No. 4)

At first, 1.84g (9.56 mmol) of 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride was added at room temperature to a solution of 1.55g (8.76 mmol) of 1-cyclopropyl-1-phenylacetic acid [Pestic-Sci., 11, 513 (1988)] and 1.80g (7.96 mmol) of 5,6-diamino-1,3-dipropyluracil in 36 ml of dioxane and 18 ml of water and the mixture was stirred for 2 hours, while adjusting the pH to 5.5. The pH of the mixture is adjusted to 7.5, and the mixture was extracted with chloroform three times, and the extract was washed with brine and dried over anhydrous sodium sulfate. Then, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent: 1.5% methanol/chloroform) to afford 2.07g (yield: 61%) of amorphous 6-amino-5-(1-cyclopropyl-1-phenyl)acetylamino-1,3-dipropyluracil [Compound (IV): R<sup>1</sup> = R<sup>2</sup> = n-C<sub>3</sub>H<sub>7</sub>;



X<sup>1</sup> = X<sup>2</sup> = O]

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 7.70 (brs, 1H), 7.40 - 7.15 (m, 5H), 5.42 (brs, 2H), 4.00 - 3.65 (m, 4H), 2.93 (d, 1H, J = 10 Hz), 1.95 - 1.25 (m, 5H), 1.10 - 0.20 (m, 10H)

Then, 30 ml of dioxane and 40 ml of an aqueous 1N sodium hydroxide solution were added to 1.90g (4.95 mmol) of the thus obtained compound and the mixture was refluxed under heating for 15 minutes. After neutralization, the mixture was concentrated until the volume of the mixture was approximately two-thirds, and the residue was extracted with chloroform three times. The extract was washed with brine and dried over anhydrous sodium sulfate. Then, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: 30% ethyl acetate/hexane) and recrystallized from cyclohexane to afford 1.77g (yield: 93%) of the captioned Compound No. 4 as a white powder. Melting point: 153.9 - 155.1 °C

Elemental analysis (C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> )	
Calculated (%):	C 68.83, H 7.15, N 15.29
Found (%):	C 69.06, H 7.42, N 15.34

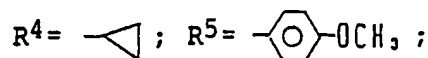
IR (KBr)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 1709, 1652, 1497

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 13.11 (brs, 1H), 7.50 - 7.40 (m, 2H), 7.35 - 7.15 (m, 3H), 4.12 (t, 2H), 3.98 (t, 2H), 3.46 (d, 1H, J = 10.3 Hz), 1.95 - 1.65 (m, 5H), 1.05 - 0.90 (m, 6H), 0.80 - 0.65 (m, 2H), 0.50 - 0.35 (m, 2H)

Example 5

## 8-[1-Cyclopropyl-1-(4-methoxyphenyl)methyl]-1,3-dipropylxanthine (Compound No. 5)

The substantially same operations as in Example 4 were repeated using 1.57g (7.61 mmol) of 1-cyclopropyl-1-(4-methoxyphenyl)acetic acid [Pestic. Sci., 11, 513 (1980)] and 1.56g (6.92 mmol) of 5,6-diamino-1,3-dipropyluracil, to afford 1.72g (yield: 53%) of amorphous 6-amino-5-[1-cyclopropyl-1-(4-methoxyphenyl)]acetyl-amino-1,3-dipropyluracil [Compound (IV);  $R^1 = R^2 = n\text{-C}_3\text{H}_7$ ;



$X^1 = X^2 = \text{O}$

NMR ( $\text{CDCl}_3$ ; 90 MHz)  $\delta$  (ppm): 7.67 (brs, 1H), 7.28 (d, 2H,  $J=9\text{ Hz}$ ), 6.83 (d, 2H,  $J=9\text{ Hz}$ ), 5.43 (brs, 2H), 4.00 - 3.70 (m, 4H), 3.79 (s, 3H), 2.92 (d, 1H,  $J=10\text{ Hz}$ ), 1.95 - 1.25 (m, 5H), 1.10 - 0.20 (m, 10H)

The substantially same operations as in Example 4 were repeated using 1.60g (3.86 mmol) of the thus obtained compound, and recrystallization from isopropanol-water afforded 1.23g (yield: 76%) of the captioned Compound No. 5 as a white needle crystal.

Melting point: 142.5 - 143.7 °C

Elemental analysis ( $\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}_3$ )	
Calculated (%):	C 66.64, H 7.12, N 14.13
Found (%) :	C 66.70, H 7.35, N 14.24

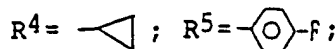
IR (KBr)  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1710, 1651, 1514, 1498

NMR ( $\text{CDCl}_3$ ; 270 MHz)  $\delta$  (ppm): 12.46 (brs, 1H), 7.38 (d, 2H,  $J=9.6\text{ Hz}$ ), 6.85 (d, 2H,  $J=9.6\text{ Hz}$ ), 4.11 (t, 2H), 3.98 (t, 2H), 3.78 (s, 3H), 3.42 (d, 1H,  $J=10.0\text{ Hz}$ ), 1.90 - 1.60 (m, 5H), 1.10 - 0.95 (m, 6H), 0.80 - 0.60 (m, 2H), 0.50 - 0.30 (m, 2H)

## Example 6

## 8-[1-Cyclopropyl-1-(4-fluorophenyl)methyl]-1,3-dipropylxanthine (Compound No. 6)

The substantially same operations as in Example 4 were repeated using 1.89g (9.73 mmol) of 1-cyclopropyl-1-(4-fluorophenyl)acetic acid [Pestic. Sci., 11, 513 (1980)] and 2.00g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil, to afford 1.91g (yield: 49%) of amorphous 6-amino-5-[1-cyclopropyl-1-(4-fluorophenyl)]acetyl-amino-1,3-dipropyluracil [Compound (IV);  $R^1 = R^2 = n\text{-C}_3\text{H}_7$ ;



$X^1 = X^2 = \text{O}$

NMR ( $\text{CDCl}_3$ ; 90 MHz)  $\delta$  (ppm): 7.73 (brs, 1H), 7.33 (dd, 2H,  $J=5, 9\text{ Hz}$ ), 7.01 (dd, 2H,  $J=9, 9\text{ Hz}$ ), 5.42 (brs, 2H), 4.00 - 3.70 (m, 4H), 2.91 (d, 1H,  $J=10\text{ Hz}$ ), 2.00 - 1.25 (m, 5H), 1.10 - 0.20 (m, 10H)

The substantially same operations as in Example 4 were repeated using 1.75g (4.35 mmol) of the thus obtained compound, and recrystallization from isopropanol-water was carried out to afford 1.41g (yield: 80%) of the captioned Compound No. 6 as a white needle crystal. Melting point: 156.2 - 157.8 °C

Elemental analysis ( $\text{C}_{21}\text{H}_{25}\text{FN}_4\text{O}_2$ )	
Calculated (%):	C 65.61, H 6.55, N 14.57
Found (%) :	C 65.57, H 6.70, N 14.69

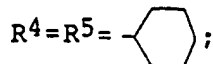
IR (KBr)  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1710, 1653, 1510, 1498

NMR ( $\text{CDCl}_3$ ; 270 MHz)  $\delta$  (ppm): 12.62 (brs, 1H), 7.45 (dd, 2H,  $J = 5.3, 8.5$  Hz), 7.01 (dd, 2H,  $J = 8.5, 8.5$  Hz), 4.12 (t, 2H), 3.98 (t, 2H), 1.90 - 1.65 (m, 5H), 1.10 - 0.95 (m, 6H), 0.80 - 0.60 (m, 4H), 0.50 - 0.35 (m, 2H)

#### Example 7

#### 8-(1,1-Dicyclohexylmethyl)-1,3-dipropylxanthine (Compound No. 7)

At first, 2.19g (9.74 mmol) of 1,1-dicyclohexylacetic acid was dissolved in 30 ml of pyridine, and then 0.78 ml (11 mmol) of thionyl chloride was added thereto. The mixture was stirred at room temperature for 30 minutes, and then a solution of 2.00g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil in 10 ml of pyridine was added thereto under ice cooling. The mixture was stirred for one hour. After addition of 50 ml of toluene thereto, the mixture was concentrated until the volume is reduced approximately to one-third and the residue was poured into ice water and extracted with chloroform three times. The extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: 1% methanol/chloroform) to afford 3.79g (yield: 99%) of amorphous 6-amino-5-(1,1-dicyclohexyl)acetylamino-1,3-dipropyluracil [Compound (IV);  $R^1 = R^2 = n\text{-C}_3\text{H}_7$ ],



$X^1 = X^2 = \text{O}$ ].

NMR ( $\text{CDCl}_3$ ; 90 MHz)  $\delta$  (ppm): 7.19 (brs, 1H), 5.52 (brs, 2H), 4.00 - 3.70 (m, 4H), 2.10 - 0.75 (m, 33H)

Then, 35 ml of phosphorus oxychloride was added to 3.50g (8.10 mmol) of the thus obtained compound and the mixture was refluxed under heating for 2 hours. After concentration under reduced pressure, the residue was poured into ice water and the pH was adjusted to 6.5 with an aqueous 2N sodium hydroxide solution. Then, the mixture was extracted with chloroform three times and the extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent: 15% ethyl acetate/hexane), and recrystallized from cyclohexane to afford 2.58g (yield: 77%) of the captioned Compound No. 7 as a white powder state.

Melting point: 198.3 - 200.1 °C

MS (m/e): 414 ( $M^+$ ), 332, 331, 289

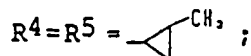
IR (KBr)  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1700, 1650, 1498

NMR ( $\text{DMSO}-d_6$ ; 270 MHz)  $\delta$  (ppm): 12.96 (brs, 1H), 3.97 (t, 2H), 3.83 (t, 2H), 2.45 (t, 1H,  $J = 7.8$  Hz), 1.90 - 0.60 (m, 32H)

#### Example 8

#### 8-[1,1-Di(2-methylcyclopropyl)methyl]-1,3-dipropylxanthine (diastereoisomer mixture) (Compound No. 8)

The substantially same operations as in Example 7 were repeated using 980 mg (5.83 mmol) of 1,1-di(2-methylcyclopropyl)acetic acid and 1.20g (5.30 mmol) of 5,6-diamino-1,3-dipropyluracil, to obtain 1.20g (yield: 60%) of amorphous 6-amino-5-[1,1-di(2-methylcyclopropyl)]acetylamino-1,3-dipropyluracil [Compound (IV);  $R^1 = R^2 = n\text{-C}_3\text{H}_7$ ];



$X^1 = X^2 = O$

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 7.58 (brs, 1H), 5.52 (brs, 2H), 4.00 - 3.75 (m, 4H), 2.00 - 0.20 (m, 25H)

885 mg (yield: 78%) of the captioned Compound No. 8 was obtained as a light yellow powder from 1.20g (3.18 mmol) of the thus obtained compound in the substantially same manner as in Example 7.

5 Melting point: 67.2 - 70.3 °C

MS (m/e): 358 (M<sup>+</sup>), 303, 287

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1700, 1655 (shoulder), 1650, 1498

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 12.65 - 12.30 (brm, 1H), 4.11 (t, 2H), 3.99 (t, 2H), 2.20 - 0.20 (m, 25H)


HPLC [AM-312(VMC 150 x 5 $\phi$ ), 50% acetonitrile-water, UV 271 nm, 2.0 ml/min]:

10 Retention time (relative area); 16.9 min.(19), 17.8 min.(30), 19.7 min.(21), 20.5 min.(30)

### Example 9

15

8-(1,1-Dicyclopropylmethyl)-1,3-dipropyl-2-thioxanthine (Compound No. 9)

The substantially same procedure as in Example 1 was repeated using 1.27g (9.09 mmol) of 1,1-dicyclopropylacetic acid and 2.00g (8.26 mmol) of 5,6-diamino-1,3-dipropyl-2-thiouracil [J. Med. Chem., 32, 1873 (1989)] to obtain 2.42g (yield: 81%) of amorphous 6-amino-5-(1,1-dicyclopropyl) acetylamino-1,3-dipropyl-2-thiouracil [Compound (IV); R<sup>1</sup> = R<sup>2</sup> = n-C<sub>3</sub>H<sub>7</sub>; R<sup>4</sup> = R<sup>5</sup> = ; X<sup>1</sup> = S; X<sup>2</sup> = O]

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 7.75 (brs, 1H), 5.70 (brs, 2H), 4.60 - 4.20 (m, 4H), 2.05 - 0.20 (m, 21H)

Then, the substantially same procedure as in Example 1 was repeated using 2.00g (5.49 mmol) of the thus obtained compound, and recrystallization was carried out from ethanol-water to afford 1.09g (yield: 57%) of the captioned Compound No. 9 as a white needle crystal.

25 Melting point: 153.8 - 156.4 °C

#### Elemental analysis (C<sub>18</sub>H<sub>26</sub>N<sub>4</sub>OS)

Calculated (%):	C 62.40, H 7.56, N 16.17
Found (%):	C 62.71, H 7.94, N 16.24

30


IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1674, 1493, 1408

35 NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 12.79 (brs, 1H), 4.69 (t, 2H), 4.57 (t, 2H), 2.00 - 1.70 (m, 5H), 1.50 - 1.35 (m, 2H), 1.10 - 0.95 (m, 6H), 0.80 - 0.60 (m, 2H), 0.50 - 0.20 (m, 6H)

### Example 10

40

8-(1,1-Dicyclopropylmethyl)-3-propylxanthine (Compound No. 10)

The substantially same procedure as in Example 1 was repeated using 1.68g (12.0 mmol) of 1,1-dicyclopropylacetic acid and 2.00g (10.9 mmol) of 5,6-diamino-3-propyluracil to afford 1.07g (yield: 51%) of 6-amino-5-(1,1-dicyclopropyl) acetylamino-3-propyluracil [Compound (IV); R<sup>1</sup> = H; R<sup>2</sup> = n-C<sub>3</sub>H<sub>7</sub>; R<sup>4</sup> = R<sup>5</sup> = ; X<sup>1</sup> = X<sup>2</sup> = O] as a pale yellow powder.

NMR (DMSO-d<sub>6</sub>; 90 MHz)  $\delta$  (ppm): 10.55 (brs, 1H), 8.16 (brs, 1H), 6.05 (brs, 2H), 3.73 (t, 2H), 1.80 - 0.10 (m, 16H)

50

To 2.00g (6.54 mmol) of the thus obtained compound were added to 40 ml of an aqueous 2N sodium hydroxide and 20 ml of dioxane. The mixture was refluxed under heating for two hours, cooled and neutralized. The neutral mixture was extracted three times with a 9:1 mixture of chloroform and methanol, and washed with brine. The mixture was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 2% methanol/chloroform), and recrystallized from ethanol to afford 859 mg (yield: 45%) of the captioned Compound No. 10 as a white crystal.

55

Melting point: 271.8 - 277.8 °C

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1694, 1660, 1499



NMR (DMSO- $d_6$ ; 90 MHz)  $\delta$  (ppm): 13.03 (brs, 1H), 10.92 (brs, 1H), 3.85 (t, 2H), 1.90 - 0.05 (m, 16H)  
 MS (m/e): 288 ( $M^+$ )

# 5 Example 11

8-(1,1-Dicyclopropylmethyl)-1,3-dipropyl-7-methylxanthine (Compound No. 11)

10 To a solution of 2.00g (6.05 mmol) of Compound No. 1 obtained in Example 1 in 60 ml of dimethylformamide were added 2.09g (15.1 mmol) of potassium carbonate and 0.75 ml (12.1 mmol) of methyl iodide. The mixture was stirred at 50 °C for one hour and cooled. Insoluble matters were filtered off, and the residue was concentrated under reduced pressure and 200 ml of water was added thereto. The aqueous solution was extracted three times with chloroform and the extract was washed with brine and  
 15 dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: 20% ethyl acetate/hexane), and recrystallized from heptane to obtain 1.71g (yield: 82%) of the captioned compound No. 11 as a white powder.  
 Melting point: 69.5 - 70.3 °C

20

Elemental analysis (C <sub>19</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub> )	
Calculated (%):	C 66.25, H 8.19, N 16.27
Found (%):	C 66.00, H 8.55, N 16.49

25

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1696, 1660, 1541, 1457

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 4.08 (t, 2H), 3.96 (t, 2H), 3.90 (s, 3H), 1.90 - 1.60 (m, 5H), 1.40 - 1.28 (m, 2H), 1.05 - 0.90 (m, 6H), 0.70 - 0.60 (m, 2H), 0.50 - 0.40 (m, 2H), 0.30 - 0.15 (m, 4H)

30

# Example 12

35 8-(1,1-Dicyclopropylmethyl)-3-propyl-6-thioxanthine (Compound No. 12)

4.00g (13.9 mmol) of Compound No. 10 obtained in Example 10 was refluxed together with 5.03g (22.6 mmol) of phosphorus pentasulfide in 80 ml of pyridine for 3 hours, and cooled. The reaction mixture was poured into 250 ml of ice water. The precipitates were separated by filtration. The filtrate was concentrated until the volume is reduced to one-fourth. The precipitate was separated by filtration, and suspended in 80  
 40 ml of an aqueous 2N sodium hydroxide and an insoluble matter was filtered off. The filtrate was neutralized, and the precipitated crystal was recrystallized from ethanol-water to afford 3.52g (yield: 83%) of the captioned compound No. 12 as a pale yellow needle crystal.

Melting point: 219.4 - 219.8 °C

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1661, 1606, 1570, 1505

45

NMR (DMSO- $d_6$ ; 90 MHz)  $\delta$  (ppm): 12.9 (brs, 1H), 12.1 (brs, 1H), 3.90 (t, 2H), 1.90 - 0.01 (m, 16H)

MS (m/e): 304 ( $M^+$ )

# 50 Example 13

7-Ethyl-8-(1,1-dicyclopropylmethyl)-1,3-dipropylxanthine (Compound No. 13)

55 The substantially same procedure as in Example 11 was repeated using 2.00g (6.5 mmol) of 8-(1,1-dicyclopropylmethyl)-1,3-dipropylxanthine obtained in Example 1 and 0.97 ml of ethyl iodide (12.1 mmol) to afford 1.53 g (yield: 71%) of the captioned Compound No. 13 as a pale yellow solid.

Melting point: 80.4 - 82.7 °C

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1700, 1659, 1539, 1417

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 4.22 (g, 2H, J=7Hz), 4.15 -3.80 (m, 4H), 1.40 (t, 3H, J=7Hz), 2.00 - 0.20 (m, 21H). MS (m/e): 358 (M<sup>+</sup>)

# 5 Example 14

8-(1,1-Dicyclopropylmethyl)-1,3-dipropyl-7-propylxanthine (Compound No. 14)

10 The substantially same procedure as in Example 11 was repeated using 2.00 g (6.05 mmol) of 8-(1,1-dicyclopropylmethyl)-1,3-dipropylxanthine obtained in Example 1 and 1.18 ml of propyl iodide (12.1 mmol), and recrystallization was carried out from ethanol-water to afford 1.85 g (yield: 82%) of the captioned Compound No. 14 as a white crystal.

Melting point: 93.2 -99.6 °C

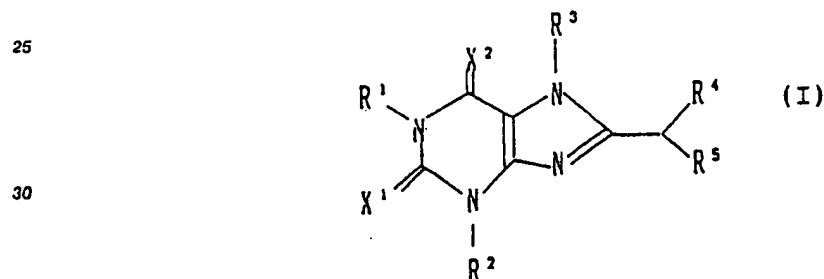
15 IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1702, 1660, 1541, 1416

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 4.25-3.75(m, 6H), 2.00-0.20(m, 26H)

MS (m/e): 372 (M<sup>+</sup>)

## 20 Claims

1. A xanthine compound represented by the following formula I



35 wherein each of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> independently represents hydrogen or lower alkyl; each of R<sup>4</sup> and R<sup>5</sup> independently represents substituted or unsubstituted alicyclic alkyl, or substituted or unsubstituted aryl; and each of X<sup>1</sup> and X<sup>2</sup> independently represents oxygen or sulfur, or its pharmaceutically acceptable salt.

40 2. The compound according to Claim 1, wherein each of R<sup>4</sup> and R<sup>5</sup> is independently selected from the group consisting of cyclopropyl, 2-methylcyclopropyl, cyclopentyl, cyclohexyl and phenyl.

3. The compound according to Claim 2, wherein both R<sup>1</sup> and R<sup>2</sup> are n-propyl and R<sup>3</sup> is hydrogen or methyl.

4. The compound according to Claim 1, which is selected from the group consisting of 8-(1,1-dicyclopropylmethyl)-1,3-dipropylxanthine, 8-(1-cyclopropyl-1-phenylmethyl)-1,3-dipropylxanthine, 8-[1,1-di-(2-methylcyclopropyl)methyl]-1,3-dipropylxanthine and 8-(1,1-dicyclopropylmethyl)-1,3-dipropyl-7-methylxanthine.

5. A pharmaceutical composition comprising a pharmaceutical carrier and, as an active ingredient, an effective amount of a xanthine compound as defined in Claim 1 or a pharmaceutically acceptable salt thereof.

6. A xanthine compound as defined in Claim 1 for use as a pharmaceutically active agent.

7. A xanthine compound as defined in Claim 1 for use as a diuretic agent, a renal-protecting agent or an antihypertensive agent.

IL



12 **EUROPEAN PATENT APPLICATION**

21 Application number: **90104201.0**

51 Int. Cl.<sup>5</sup>: **C07D 473/06, C07D 473/22, A61K 31/52**

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**12.09.90 Bulletin 90/37**

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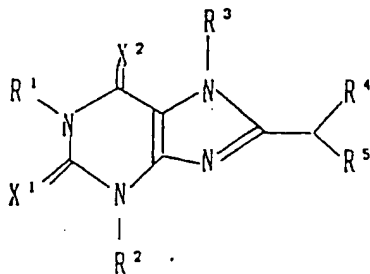
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54 **Xanthine derivatives.**

57 Novel xanthine compounds represented by the following formula:

protecting agent and an antihypertensive agent.



and pharmaceutically acceptable salts thereof have a diuretic action, a renal-protecting action and a vasodilative action.

The compounds are useful as a diuretic, a renal-



European  
Patent Office

## EUROPEAN SEARCH REPORT

Application Number

EP 90 10 4201

DOCUMENTS CONSIDERED TO BE RELEVANT					
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)		
A	EP-A-0 215 736 (SANDOZ AG) * Pages 18-20; claims 1-8 * -----	1-7	C 07 D 473/06 C 07 D 473/22 A 61 K 31/52		
			TECHNICAL FIELDS SEARCHED (Int. Cl.8)		
			C 07 D 473/00		
The present search report has been drawn up for all claims					
Place of search The Hague		Date of completion of search 11 November 91	Examiner LUYTEN H.		
<table><tr><td><b>CATEGORY OF CITED DOCUMENTS</b> X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention</td><td>E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons ..... &amp;: member of the same patent family, corresponding document</td></tr></table>				<b>CATEGORY OF CITED DOCUMENTS</b> X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention	E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons ..... &: member of the same patent family, corresponding document
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(54) **Xanthine derivatives**

Xanthinderivate

Dérivés de xanthine

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(56) References cited:  
**EP-A- 0 215 736**

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**EP 0 386 675 B1**

## Description

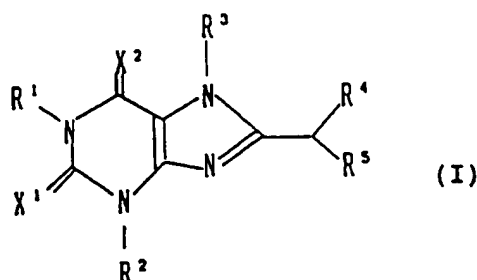
The present invention relates to novel xanthine derivatives having diuretic action, renal-protecting action and vasodilative action.

Heretofore, theophylline, i.e., 1,3-dimethylxanthine has been known as a diuretic, a vasodilator, etc. [The Merck Index, 10th edition, 9114 (1983)].

Theophylline analogues represented by the following general formula (I) wherein both R<sup>4</sup> and R<sup>5</sup> are alkyl have a diuretic action, as disclosed in East German Patent No. 31,772 [Chem. Abst., 63, 18120d (1965)] (CA-724,173A); J. Am. Chem. Soc., 75, 114 (1953) and J. Med. Chem., 14, 1202 (1971), and also have a bronchodilative action, as disclosed in JP-A- 166191/81 (US-A-4,546,182), JP-A-163381/82 (GB-A-2091249) and JP-A-41478/88 (EP-A-256692). Furthermore, xanthine derivatives having an anti-inflammatory action and other activities are disclosed in JP-A-66583/80 (US-A-4,299,832); Japanese National Publication of translated version No. 500666/86 (US-A-4,558,051); US-A-3,624,215 and 3,624,216.

The present invention provides novel xanthine derivatives represented by the formula (I) wherein R<sup>4</sup> and R<sup>5</sup> are alicyclic alkyl or aryl groups and having diuretic action, renal-protecting action, vasodilative action, etc.

The present invention relates to xanthine derivatives represented by the following general formula (I):



wherein each of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> independently represents hydrogen or lower alkyl; each of R<sup>4</sup> and R<sup>5</sup> independently represents substituted or unsubstituted alicyclic alkyl, or substituted or unsubstituted aryl; and each of X<sup>1</sup> and X<sup>2</sup> independently represents oxygen or sulfur [hereinafter referred to as "Compound (I)" and compounds with other formula numbers are likewise referred to], or pharmaceutically acceptable salts thereof.

In the definition of the respective groups in the formula (I), the lower alkyl includes straight or branched alkyl having 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, etc. The alicyclic alkyl includes those having 3 to 8 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, etc. The aryl includes phenyl, naphthyl, etc. The substituent on the alicyclic alkyl and aryl independently includes lower alkyl, hydroxy, lower alkoxy, halogen, amino, nitro, etc., and the number of the substituents is 1 to 3. As the lower alkyl and the alkyl moiety in the lower alkoxy, mention may be made of the same groups as defined in the aforementioned lower alkyl. The halogen includes fluorine, chlorine, bromine and iodine.

The pharmaceutically acceptable salts of Compound (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, amino acid addition salts, etc.

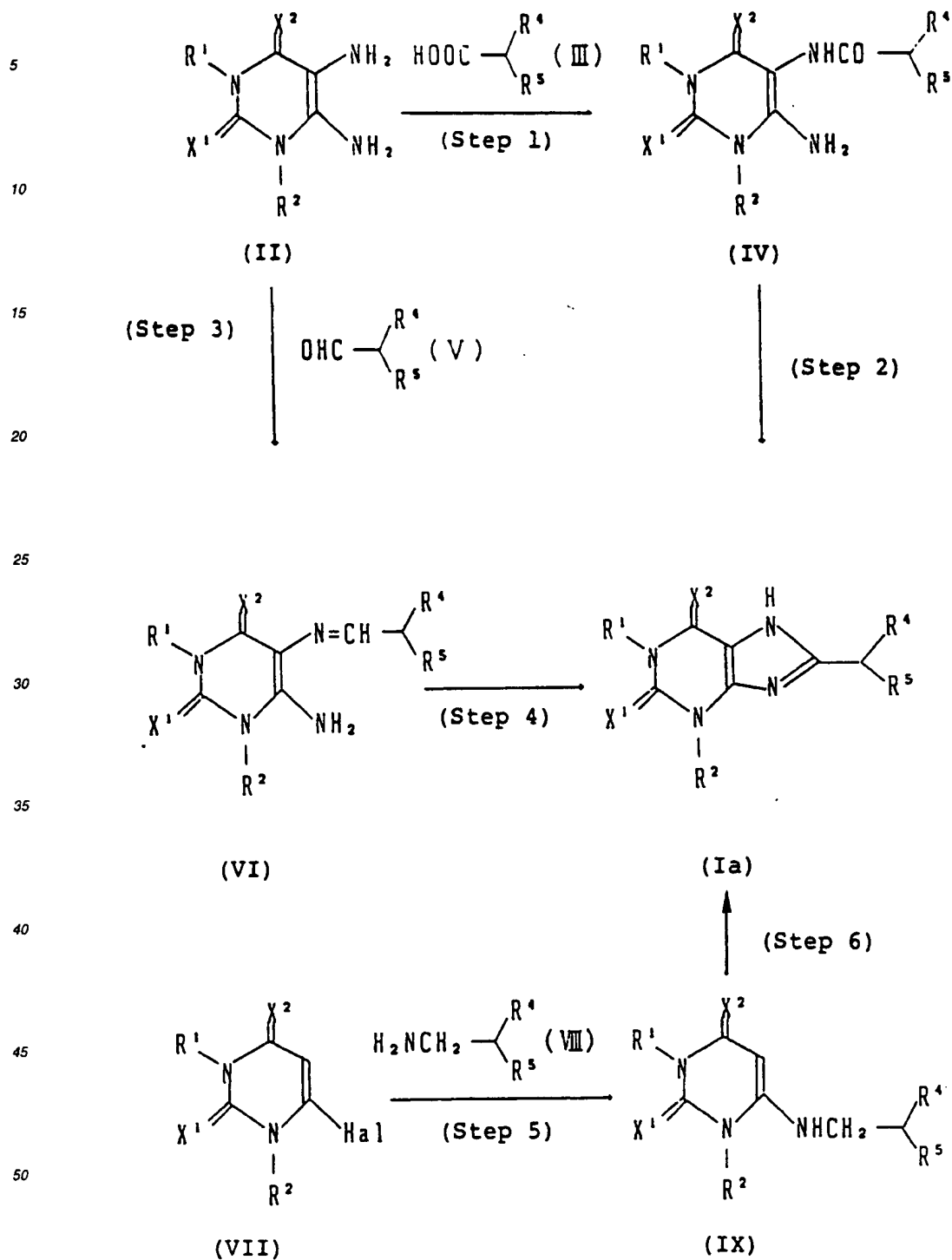
The pharmaceutically acceptable acid addition salts of Compound (I) include inorganic acid salts such as hydrochlorides, sulfates, phosphates, etc., and organic acid salts such as acetates, maleates, fumarates, oxalates, citrates, etc.

The pharmaceutically acceptable metal salts include alkali metal salts such as sodium salts, potassium salts, etc., alkaline earth metal salts such as magnesium salts, calcium salts etc., and also aluminum and zinc salts.

The ammonium salts include salts of ammonium, tetramethylammonium, etc. The pharmaceutically acceptable organic amine addition salts include addition salts of morpholine, piperidine, etc., and the pharmaceutically acceptable amino acid addition salts include addition salts of lysine, glycine, phenylalanine, etc.

A process for producing the compounds of the present invention will be described below.

Compound (Ia) which is Compound (I) wherein R<sup>3</sup> is hydrogen, can be produced by the following production steps:



wherein Hal represents halogen such as chlorine, bromine or iodine and R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, X<sup>1</sup> and X<sup>2</sup> have the same meanings as defined above.

Step 1:

A Compound (IV) can be obtained by reacting a uracil derivative (II) obtained according to a well known process [for example, the process disclosed in JP-A- 42383/84] with carboxylic acid (III) or a carboxylic acid reactive derivative.

The carboxylic acid reactive derivative includes acid halides such as acid chlorides, acid bromides, etc., active esters such as p-nitrophenyl ester, N-oxy succinimide ester, etc., acid anhydrides commercially available or those formed from carbodiimides such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diisopropylcarbodiimide, dicyclohexylcarbodiimide, etc.; mixed acid anhydrides with monoethyl carbonate, monoisobutyl carbonate, etc. and so forth.

The reaction of Compound (II) with Compound (III) can be carried out without any solvent at a temperature of 50 to 200°C. In the case of using the carboxylic acid reactive derivative, the reaction can be carried out according to a process usually used in the peptide chemistry. For example, the reaction solvent is properly selected from halogenohydrocarbons such as methylene chloride, chloroform, dichloroethane, etc., ethers such as dioxane, tetrahydrofuran, etc., dimethylformamide and dimethylsulfoxide, and if necessary water is used. The reaction temperature is -80 to 50°C, and the reaction is completed for 0.5 to 24 hours. Sometimes, the reaction may be favorably carried out, if necessary, in the presence of an additive such as 1-hydroxybenzotriazole, etc., or a base such as pyridine, triethylamine, dimethylaminopyridine, N-methylmorpholine, etc. Furthermore, the carboxylic acid reactive derivative may be formed in the reaction system and used without isolation.

Step 2:

A desired Compound (Ia) with a closed ring can be obtained from Compound (IV) by the reaction in the presence of a base (process A), by treatment with a dehydrating agent (process B), or by heating (process C).

As the preferable base in the process A, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, etc. can be exemplified. As the reaction solvent, water, lower alcohols such as methanol, ethanol, etc., ethers such as dioxane, tetrahydrofuran, etc., dimethylformamide, dimethylsulfoxide, etc. can be used alone or in combination. The reaction is carried out at a temperature of from room temperature to 180°C and is usually completed for 10 minutes to 6 hours.

As the dehydrating agent for use in the process B, thionyl halides such as thionyl chloride, etc., and phosphorus oxyhalides such as phosphorus oxychloride, etc. can be used, and the reaction is carried out at a temperature of from room temperature to 180°C without any solvent or in a solvent inert to the reaction, for example, halogenohydrocarbons such as methylene chloride, chloroform, dichloroethane, etc., dimethylformamide, dimethylsulfoxide, etc. and is usually completed for 0.5 to 12 hours.

In the case of process C, the Compound (Ia) can be obtained by heating Compound (IV) at a temperature of 50 to 200°C in a polar solvent such as dimethylsulfoxide, dimethylformamide, Dowthermo A (product of Muromachi Kagaku Kogyo Kaisha, Ltd.), etc.

Step 3:

A Schiff base (VI) can be obtained by reacting Compound (II) with aldehyde (V) in a mixed solvent such as a mixture of acetic acid with a lower alcohol such as methanol, ethanol, etc. at a temperature of -20 to 100°C.

Step 4:

A desired Compound (Ia) can be obtained by subjecting Compound (VI) to an oxidative cyclization reaction.

As the appropriate oxidizing agent, oxygen, ferric chloride, cerium<sup>IV</sup> ammonium nitrate, diethyl azodicarboxylate, etc. can be exemplified. The reaction is carried out by heating Compound (VI) at from room temperature to 180°C in the presence of the afore-mentioned oxidizing agent and, if necessary, in a solvent inert to the reaction, for example, a lower alcohol such as methanol, ethanol, etc., a halogenohydrocarbon such as methylene chloride, chloroform, etc., or an aromatic hydrocarbon such as toluene, xylene, nitrobenzene, etc.

Step 5:

A Compound (IX) can be obtained by reacting a uracil derivative (VII) obtained according to a well known process, for example, the process described in Japanese Published Unexamined Patent Application No. 5082/86 with an amine (VIII) in a solvent inert to the reaction, for example, a lower alcohol such as methanol, ethanol, etc., dimethylformamide, dimethylsulfoxide, etc. alone or in combination thereof at a temperature of 50 to 150°C.

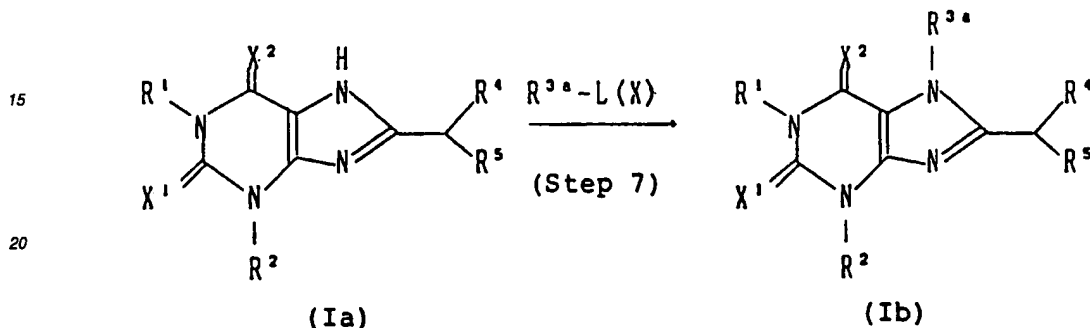


Step 6:

A Compound (Ia) can be obtained by reacting a Compound (IX) with a nitrosating agent such as a nitrite derivative such as sodium nitrite, isoamyl nitrite, etc. under an acidic condition of dilute hydrochloric acid, etc. in a solvent inert to the reaction, for example, a lower alcohol such as methanol, ethanol, etc. usually at a temperature of from room temperature to the boiling point of the solvent.

Step 7:

A Compound (Ib) which is Compound (I) wherein R<sup>3</sup> is a lower alkyl group can be obtained through the following step:



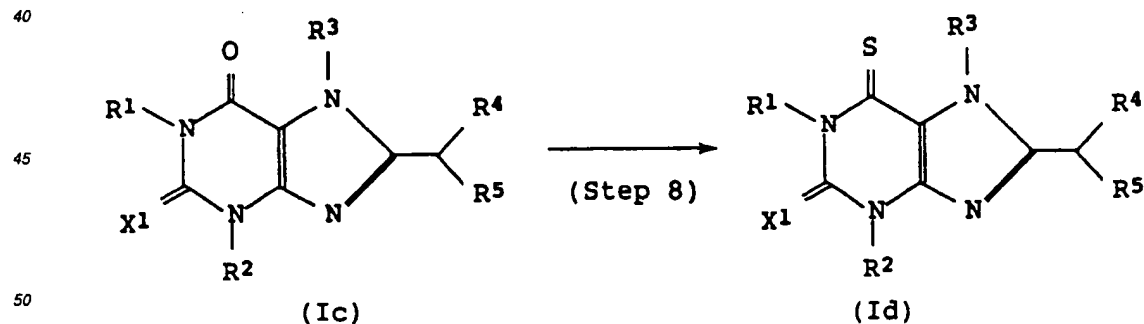
wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, X<sup>1</sup> and X<sup>2</sup> have the same meanings as defined above, R<sup>3a</sup> represents a lower alkyl in the definition of R<sup>3</sup> and L represents a leaving group.

As the leaving group, halogen such as bromine, iodine, etc., alkylsulfonyloxy such as methanesulfonyloxy, etc., and arylsulfonyloxy such as p-toluenesulfonyloxy, etc. can be exemplified.

A desired compound (Ib) can be obtained by reacting Compound (Ia) obtained in Steps 1 to 6 with an alkylating agent (X) preferably in the presence of a base. As the base, an alkali metal carbonate such as sodium carbonate, potassium carbonate, etc., an alkali metal hydride such as sodium hydride, etc., and an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, etc. can be exemplified. The reaction is completed at a temperature of 0 to 180°C usually for 0.5 to 24 hours.

Step 8:

Compound (Id) which is Compound (I) wherein X<sup>2</sup> is sulfur, can be obtained according to the following step.



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and X<sup>1</sup> have the same meanings as previously defined.

A desired Compound (Id) was prepared by reacting Compound (Ic) obtained by the above-mentioned steps which is Compound (I) wherein X<sup>2</sup> is oxygen, with an appropriate thionation reagent, in an inert solvent. As the thionation reagent, phosphorus pentasulfide and the like are mentioned. As the solvent, dimethylformamide, tetrahydrofuran, dioxane, etc. are mentioned, and preferably pyridine and the like are used. The reaction is carried out at a temperature of 50 to 180°C for a period of 10 minutes to 12 hours.

The intermediates and the desired compounds obtained according to the aforementioned processes can be isolated and purified by subjecting them to a purification process usually used in the organic synthetic chemistry, for example, filtration, extraction, washing, drying, concentration, recrystallization, various chromatographies, etc. The intermediates can be used in the successive reaction without any purification.

5        Salts of Compounds (I) can be obtained by direct purification when Compound (I) can be obtained in a salt form, or by formation of a salt according to a usual procedure when the Compound (I) is obtained in a free form, and a subsequent purification.

Compounds (I) and their pharmaceutically acceptable salts sometimes exist in an adduct form with water or various other solvents, and these adducts are included in the present invention.

10        Optical isomers may exist with respect to Compounds (I), and all the possible stereoisomers and their mixtures are also included in the scope of the present invention.

Specific examples of Compounds (I) are shown in Table 1, where compound numbers correspond to Example numbers appearing hereinafter:

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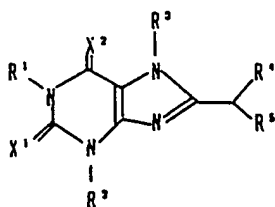
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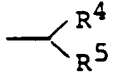




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Table 1



Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>		X <sup>1</sup>	X <sup>2</sup>
1	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
2	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
3	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
4	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
5	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
6	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
7	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
8	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		O	O
9	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	H		S	O
10	H	n-C <sub>3</sub> H <sub>7</sub>	H		O	O

Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>		X <sup>1</sup>	X <sup>2</sup>
11	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>		O	O
12	H	n-C <sub>3</sub> H <sub>7</sub>	H		O	S
13	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	C <sub>2</sub> H <sub>5</sub>		O	O
14	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>3</sub> H <sub>7</sub>		O	O

Compounds (I) of the present invention and their pharmaceutically acceptable salts have diuretic action, renal-protecting action and vasodilative action and thus Compounds (I) are useful as a diuretic, a renal-protecting agent and an antihypertensive agent.

The pharmacological action of Compounds (I) will be explained, referring to Test Examples.

#### Test Example 1, diuretic action

Wistar rats (male: 150 - 300 g) were starved for 18 hours prior to the administration of the test compound. A test compound (25 mg/kg) and saline (25 ml/kg) were orally administered to test rats and only saline was administered to control rats. Three groups, each group consisting of 3 rats, were used for each test compound. Urine was collected for 6 hours after the administration. Urine volume was measured and the electrolytes (Na and K) in the urine were determined with a flame photometer (775A, Hitachi, Ltd., Japan). The results are shown in Table 2.

All parameters are expressed as relative values of control. The compounds Nos. 1, 4 and 11 exhibited more potent activity in the urine volume and have much higher ratios of Na to K than the reference compounds.

Table 2

Compound No.	Urine amount (%)	Na <sup>+</sup> excretion (%)	K <sup>+</sup> excretion (%)	Na <sup>+</sup> /K <sup>+</sup>
(Control)	100	100	100	1.00
1	244	216	127	1.71
2	102	96	88	1.08
3	128	129	101	1.28
4	198	221	123	1.83
8	124	119	113	1.05
11	280	180	92	1.46
Aminophylline <sup>*1</sup> (Reference compound)	134	189	117	1.62
Furosemide <sup>*2</sup> (Reference compound)	175	164	157	1.05

\*1 The Merck Index, 10th edition, page 476 (1983)

\*2 The Merck Index, 10th edition, page 4189 (1983)

Test Example 2, renal-protecting action (glycerol-induced renal failure model).

A renal failure is a state where the renal function is lowered and the stationary state of a body fluid can be no more maintained. It is known that an acute renal failure characteristic of uriniferous tubule disorder is caused by subcutaneous or intramuscular injection of glycerol to rats [Can. J. Physiol. Pharmacol., 65, 42 (1987)].

Wistar rats (male) were kept deprived of water for 18 hours, and served for the test. A test compound was intraperitoneally administered to the rats (dosage: 10 mg/kg) and the rats were anesthetized with ether and 50% glycerol was subcutaneously administered (dosage: 0.8 ml/100g) to the rats, pinching the dorsal skin. Twenty four hours after the administration of glycerol, the rats were anesthetized with ether and 5 ml of blood was collected from the abdominal aorta. The collected blood was allowed to stand for 30 minutes or longer and then centrifuged at 3,000 rpm for 10 minutes, and the serum creatinine was measured by creatinine test Wako (Jaffé method).

On the other hand, the left kidneys of the blood-sampled rats were removed and placed in formalin-filled vial bottles, and used as samples for the pathological examination.

According to the test results, Compounds Nos. 1, 8 and 11 significantly suppressed an increase in the serum creatinine at a dosage of 10 mg/kg [i.p.] (Compound No. 1:  $p < 0.05$ ; Compound No. 8:  $p < 0.001$ ; Compound No. 11:  $p < 0.001$ ), whereas aminophylline had no substantial effect of suppressing the increase. On the contrary, furosemide showed a tendency to increase the serum creatinine. The pathological examination of removed kidneys indicates that compounds Nos. 1, 8 and 11 also significantly improved the state of kidneys.

Compounds (I) or their pharmaceutically acceptable salts can be used as such or in various medicament forms. The present pharmaceutical composition can be prepared by uniformly mixing an effective amount of Compound (I) or its pharmaceutically acceptable salts as an active component with a pharmaceutically acceptable carrier. The pharmaceutical composition is desirably in a unit dosage form applicable to oral or injection administration.

In the preparation of pharmaceutical compositions in an oral dosage form, some useful, pharmaceutically acceptable carrier can be used. For example, liquid, orally administerable compositions such as suspension compositions or syrup compositions can be prepared with water, a saccharide such as sucrose, sorbitol, fructose, etc., a glycol such as polyethyleneglycol, propyleneglycol, etc., an oil such as sesame oil, olive oil, soybean oil, etc., an antiseptic such as p-hydroxybenzoic acid esters, etc., and a flavor such as strawberry flavor, peppermint, etc. Powder, pills, capsules and tablets can be prepared with a vehicle such as lactose, glucose, sucrose, mannitol, etc., a disintegrator such as starch, sodium alginate, etc., a lubricant such as magnesium stearate, talc, etc., a binder such as polyvinyl alcohol, hydroxypropyl cellulose, gelatin, etc., a surfactant such as fatty acid esters, etc., a plasticizer such as glycerin, etc. and so forth. Tablets and capsules are most useful unit for oral administration because of easy administration. In the preparation of tablets or capsules, a solid pharmaceutical carrier is used.

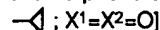
Injection solutions can be prepared with a carrier such as distilled water, saline solution, glucose solution, or a mixture of saline solution and glucose solution.

Effective dosage and number of administrations of a Compound (I) or its pharmaceutically acceptable salts depend on the administration route and ages, body weights, symptoms, etc. of patients, and it is preferable to usually administer Compound (I) at a dosage of 1 to 50 mg/kg per day in 3 to 4 divisions.

The present invention will be described below, referring to Examples.

## Example 1

## 8-(1,1-Dicyclopropylmethyl)-1,3-dipropylxanthine (Compound No. 1)

At first, 1.40g (10 mmol) of 1,1-dicyclopropylacetic acid was dissolved in 25 ml of pyridine, and 0.78 ml (11 mmol) of thionyl chloride was added thereto. Then, the mixture was stirred at 60°C for 10 minutes. Then, a solution of 2.26g (10 mmol) of 5,6-diamino-1,3-dipropyluracil in 15 ml of pyridine was added thereto under ice cooling, and the mixture was stirred for one hour. Then, the solvent was concentrated to approximately one-half under reduced pressure and the residue was poured into ice water and subjected to extraction with chloroform three times. The extract was washed with brine, and dried over anhydrous sodium sulfate and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% methanol/chloroform) to afford 2.33g (yield: 67%) of amorphous 6-amino-5-(1,1-dichloropropyl)acetyl-amino-1,3-dipropyluracil (Compound (IV):  $R^1=R^2=n-C_3H_7$ ;  $R^4=R^5=$  ;  $X^1=X^2=O$ )

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm) : 7.71 (brs, 1H), 5.52 (brs, 2H), 4.00 - 3.75 (m, 4H), 1.90 - 1.50 (m, 4H), 1.40 - 0.20 (m, 17H)

Then, 10 ml of phosphorus oxychloride was added to the thus obtained compound and the mixture was refluxed for two hours. After concentration under reduced pressure, the residue was poured into ice water and the pH was adjusted to 6.5 with an aqueous 2N sodium hydroxide solution. Then, the mixture was extracted with chloroform three times, and the combined extract was washed with brine and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 30% ethyl ace-

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tate/hexane) and recrystallized from ethanol-water to afford 1.33g (yield: 60%) of the captioned Compound No. 1 as a white needle crystal.

Melting point: 129.1 - 130.4°C

Elemental analysis (C <sub>18</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> )			
Calculated (%):	C 65.43,	H 7.93,	N 16.96
Found (%) :	C 65.53,	H 8.11,	N 16.82

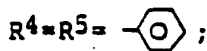
IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1700, 1654, 1498

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 12.70 (brs, 1H), 4.13 (t, 2H), 3.97 (t, 2H), 1.90 - 1.60 (m, 5H), 1.50 - 1.35. (m, 2H), 1.10 - 0.90 (m, 6H), 0.75 - 0.60 (m, 2H), 0.50 - 0.20 (m, 6H)

## Example 2

8-(1,1-Diphenylmethyl)-1,3-dipropylxanthine (Compound No. 2)

At first, 2.00g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil was dissolved in 10 ml of pyridine and 2.45g (10.6 mmol) of diphenylacetyl chloride was added thereto under ice cooling. After stirring for 40 minutes, the mixture was poured into ice water and extracted with toluene three times. The extract was successively washed with water, an aqueous saturated sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford 3.92g of amorphous 6-amino-5-(1,1-diphenyl)acetylamino-1,3-dipropyluracil [Compound (IV): R<sup>1</sup>=R<sup>2</sup>=n-C<sub>3</sub>H<sub>7</sub>;



X<sup>1</sup>=X<sup>2</sup>=O]

Then, 36 ml of dioxane and 36 ml of an aqueous 2N sodium hydroxide solution were added to 3.62g of the thus obtained compound and the mixture was refluxed under heating for 35 minutes. After cooling, the mixture was neutralized and extracted with chloroform three times. Then, the extract was washed with brine and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, and recrystallized from cyclohexane to afford 2.53g (total yield: 86%) of the captioned Compound No. 2 as a white powder.

Melting point: 167.1 - 168.5°C

Elemental analysis (C <sub>24</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> )			
Calculated (%):	C 71.62,	H 6.51,	N 13.92
Found (%) :	C 71.65,	H 6.51,	N 13.70

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1708, 1649, 1557, 1493

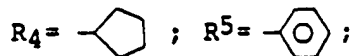
NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 7.35 - 7.05 (m, 10H), 5.68 (s, 1H), 4.20 - 3.75 (m, 4H), 1.95 - 1.45 (m, 4H), 1.10 - 0.80 (m, 6H)

## Example 3

8-(1-Cyclopentyl-1-phenylmethyl)-1,3-dipropylxanthine (Compound No. 3)

At first, 2.17g (10.62 mmol) of 2-phenylcyclopentane acetic acid and 2.04g (10.62 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride were added to a solution of 2.00g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil in 40 ml of dioxane and 20 ml of water and the mixture was stirred at room temperature for 4 hours while adjusting the pH to 5.5. The pH of the mixture was adjusted to pH 7.5, and then the mixture was extracted with chloroform three times, and the extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 2% methanol/chloroform) to

afford 1.73g (yield: 47%) of amorphous 6-amino-5-(1-cyclopentyl-1-phenyl)acetyl-amino-1,3-dipropyluracil [Compound (IV):  $R^1=R^2=n\text{-C}_3\text{H}_7$ ;



$X^1=X^2=O$ ]

MS (m/e): 412, 253, 226, 225, 159, 91

NMR ( $\text{CDCl}_3$ ; 90 MHz)  $\delta$ (ppm): 7.50 - 7.00 (m, 5H), 5.22 (brs, 2H), 4.00 - 3.60 (m, 4H), 3.28 (d, 1H,  $J=11$  Hz), 2.8 - 2.45 (m, 1H), 2.10 - 0.80 (m, 18H)

Then, 13 ml of phosphorus oxychloride was added to 1.28g (3.11 mmol) of the thus obtained compound and the mixture was refluxed under heating for 30 minutes. Then, the mixture was concentrated under reduced pressure and the residue was poured into ice water. The pH was adjusted to 6.5 with an aqueous 2N sodium hydroxide solution. The mixture was extracted with chloroform three times and the extract was washed with brine and dried over anhydrous sodium sulfate. Then, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: 25% ethyl acetate/hexane), and recrystallized from isopropanol-water to afford 730 mg (yield: 59%) of the captioned Compound No. 3 as a white powder.

Melting point: 136.6 - 138.1°C


Elemental analysis ( $\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_2$ )			
Calculated (%):	C 70.02,	H 7.66,	N 14.20
Found (%) :	C 69.91,	H 7.77,	N 14.14

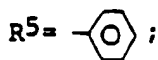
IR (KBr)  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) : 1703, 1654, 1496

NMR ( $\text{CDCl}_3$ ; 270 MHz)  $\delta$  (ppm) : 12.80 (brs, 1H), 7.60 - 7.15 (m, 5H), 4.20 - 4.05 (m, 4H), 3.90 (d, 1H,  $J=11.0$  Hz), 3.10 - 2.90 (m, 1H), 2.00 - 1.50 (m, 10H), 1.30 - 0.90 (m, 8H)

#### Example 4

#### 8-(1-Cyclopropyl-1-phenylmethyl)-1,3-dipropylxanthine (Compound No. 4)

At first, 1.84g (9.56 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added at room temperature to a solution of 1.55g (8.76 mmol) of 1-cyclopropyl-1-phenylacetic acid [Pestic-Sci., 11, 513 (1988)] and 1.80g (7.96 mmol) of 5,6-diamino-1,3-dipropyluracil in 36 ml of dioxane and 18 ml of water and the mixture was stirred for 2 hours, while adjusting the pH to 5.5. The pH of the mixture was adjusted to 7.5, and the mixture was extracted with chloroform three times, and the extract was washed with brine and dried over anhydrous sodium sulfate. Then, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent: 1.5% methanol/chloroform) to afford 2.07g (yield: 61%) of amorphous 6-amino-5-(1-cyclopropyl-1-phenyl)acetyl-amino-1,3-dipropyluracil [Compound (IV):  $R^1=R^2=n\text{-C}_3\text{H}_7$ ;  $R^4=$  ;



$X^1=X^2=O$ ]

NMR ( $\text{CDCl}_3$ ; 90 MHz)  $\delta$ (ppm) : 7.70 (brs, 1H), 7.40 - 7.15 (m, 5H), 5.42 (brs, 2H), 4.00 - 3.65 (m, 4H), 2.93 (d, 1H,  $J=10$  Hz), 1.95 - 1.25 (m, 5H), 1.10 - 0.20 (m, 10H)

Then, 30 ml of dioxane and 40 ml of an aqueous 1N sodium hydroxide solution were added to 1.90g (4.95 mmol) of the thus obtained compound and the mixture was refluxed under heating for 15 minutes. After neutralization, the mixture was concentrated until the volume of the mixture was approximately two-thirds, and the residue was extracted with chloroform three times. The extract was washed with brine and dried over anhydrous sodium sulfate. Then, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: 30% ethyl acetate/hexane) and recrystallized from cyclohexane to afford 1.77g (yield: 93%) of the captioned Compound No. 4 as a white powder.

Melting point: 153.9 - 155.1°C


Elemental analysis (C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> )			
Calculated (%):	C 68.83,	H 7.15,	N 15.29
Found (%) :	C 69.06,	H 7.42,	N 15.34

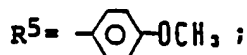
IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1709, 1652, 1497

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$ (ppm): 13.11 (brs, 1H), 7.50 - 7.40 (m, 2H), 7.35 - 7.15 (m, 3H), 4.12 (t, 2H), 3.98 (t, 2H), 3.46 (d, 1H, J=10.3 Hz), 1.95 - 1.65 (m, 5H), 1.05 - 0.90 (m, 6H), 0.80 - 0.65 (m, 2H), 0.50 - 0.35 (m, 2H)

#### Example 5

#### 8-[1-Cyclopropyl-1-(4-methoxyphenyl)methyl]-1,3-dipropylxanthine (Compound No. 5)

The substantially same operations as in Example 4 were repeated using 1.57g (7.61 mmol) of 1-cyclopropyl-1-(4-methoxyphenyl)acetic acid [Pestic. Sci., 11, 513 (1980)] and 1.56g (6.92 mmol) of 5,6-diamino-1,3-dipropyluracil, to afford 1.72g (yield: 53%) of amorphous 6-amino-5-[1-cyclopropyl-1-(4-methoxyphenyl)]acetylamino-1,3-dipropyluracil [Compound (IV): R<sup>1</sup>=R<sup>2</sup>=n-C<sub>3</sub>H<sub>7</sub>; R<sup>4</sup>= 



X<sup>1</sup>=X<sup>2</sup>=O]

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$ (ppm): 7.67 (brs, 1H), 7.28 (d, 2H, J=9Hz), 6.83 (d, 2H, J=9 Hz), 5.43 (brs, 2H), 4.00 - 3.70 (m, 4H), 3.79 (s, 3H), 2.92 (d, 1H, J=10 Hz), 1.95 - 1.25 (m, 5H), 1.10 - 0.20 (m, 10H)

The substantially same operations as in Example 4 were repeated using 1.60g (3.86 mmol) of the thus obtained compound, and recrystallisation from isopropanol-water afforded 1.23g (yield: 76%) of the captioned Compound No. 5 as a white needle crystal.

Melting point: 142.5 - 143.7°C


Elemental analysis (C <sub>22</sub> H <sub>28</sub> N <sub>4</sub> O <sub>3</sub> )			
Calculated (%):	C 66.64,	H 7.12,	N 14.13
Found (%) :	C 66.70,	H 7.35,	N 14.24

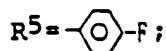
IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1710, 1651, 1514, 1498

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 12.46 (brs, 1H), 7.38 (d, 2H, J=9.6 Hz), 6.85 (d, 2H, J=9.6 Hz), 4.11 (t, 2H), 3.98 (t, 2H), 3.78 (s, 3H), 3.42 (d, 1H, J=10.0 Hz), 1.90 - 1.60 (m, 5H), 1.10 - 0.95 (m, 6H), 0.80 - 0.60 (m, 2H), 0.50 - 0.30 (m, 2H)

#### Example 6

#### 8-[1-Cyclopropyl-1-(4-fluorophenyl)methyl]-1,3-dipropylxanthine (Compound No. 6)

The substantially same operations as in Example 4 were repeated using 1.89g (9.73 mmol) of 1-cyclopropyl-1-(4-fluorophenyl)acetic acid [Pestic. Sci., 11, 513 (1980)] and 2.00g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil, to afford 1.91g (yield: 49%) of amorphous 6-amino-5-[1-cyclopropyl-1-(4-fluorophenyl)]acetylamino-1,3-dipropyluracil [Compound (IV): R<sup>1</sup>=R<sup>2</sup>=n-C<sub>3</sub>H<sub>7</sub>; R<sup>4</sup>= 



X<sup>1</sup>=X<sup>2</sup>=O].

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 7.73 (brs, 1H), 7.33 (dd, 2H, J=5, 9 Hz), 7.01 (dd, 2H, J=9, 9 Hz), 5.42 (brs, 2H),



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4.00 - 3.70 (m, 4H), 2.91 (d, 1H, J=10 Hz), 2.00 - 1.25 (m, 5H), 1.10 - 0.20 (m, 10H)

The substantially same operations as in Example 4 were repeated using 1.75g (4.35 mmol) of the thus obtained compound, and recrystallization from isopropanol-water was carried out to afford 1.41g (yield: 80%) of the captioned Compound No. 6 as a white needle crystal.

Melting point: 156.2 - 157.8°C

Elemental analysis (C <sub>21</sub> H <sub>25</sub> FN <sub>4</sub> O <sub>2</sub> )			
Calculated (%):	C 65.61,	H 6.55,	N 14.57
Found (%):	C 65.57,	H 6.70,	N 14.69

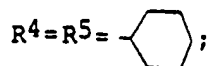
IR (KBr)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 1710, 1653, 1510, 1498

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 12.62 (brs, 1H), 7.45 (dd, 2H, J=5.3, 8.5 Hz), 7.01 (dd, 2H, J=8.5 8.5 Hz), 4.12 (t, 2H), 3.98 (t, 2H), 1.90 - 1.65 (m, 5H), 1.10 - 0.95 (m, 6H), 0.80 - 0.60 (m, 4H), 0.50 - 0.35 (m, 2H)

## Example 7

8-(1,1-Dicyclohexylmethyl)-1,3-dipropylxanthine (Compound No. 7)

At first, 2.19g (9.74 mmol) of 1,1-dicyclohexylacetic acid was dissolved in 30 ml of pyridine, and then 0.78 ml (11 mmol) of thionyl chloride was added thereto. The mixture was stirred at room temperature for 30 minutes, and then a solution of 2.00g (8.85 mmol) of 5,6-diamino-1,3-dipropyluracil in 10 ml of pyridine was added thereto under ice cooling. The mixture was stirred for one hour. After addition of 50 ml of toluene thereto, the mixture was concentrated until the volume is reduced approximately to one-third and the residue was poured into ice water and extracted with chloroform three times. The extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: 1% methanol/chloroform) to afford 3.79g (yield: 99%) of amorphous 6-amino-5-(1,1-dicyclohexyl)acetyl-amino-1,3-dipropyluracil [Compound (IV): R<sup>1</sup>=R<sup>2</sup>=n-C<sub>3</sub>H<sub>7</sub>,



X<sup>1</sup>=X<sup>2</sup>=O].

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 7.19 (brs, 1H), 5.52 (brs, 2H), 4.00 - 3.70 (m, 4H), 2.10 - 0.75 (m, 33H)

Then, 35 ml of phosphorus oxychloride was added to 3.50g (8.10 mmol) of the thus obtained compound and the mixture was refluxed under heating for 2 hours. After concentration under reduced pressure, the residue was poured into ice water and the pH was adjusted to 6.5 with an aqueous 2N sodium hydroxide solution. Then, the mixture was extracted with chloroform three times and the extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent: 15% ethyl acetate/hexane), and recrystallised from cyclohexane to afford 2.58g (yield: 77%) of the captioned Compound No. 7 as a white powder state.

Melting point: 198.3 - 200.1°C

MS (m/e): 414 (M<sup>+</sup>), 332, 331, 289

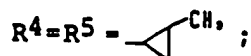
IR (KBr)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 1700, 1650, 1498

NMR (DMSO-d<sub>6</sub>; 270 MHz)  $\delta$  (ppm): 12.96 (brs, 1H), 3.97 (t, 2H), 3.83 (t, 2H), 2.45 (t, 1H, J=7.8 Hz), 1.90 - 0.60 (m, 32H)

## Example 8

8-[1,1-Di(2-methylcyclopropyl)methyl]-1,3-dipropylxanthine (diastereoisomer mixture) (Compound No. 8)

The substantially same operations as in Example 7 were repeated using 980 mg (5.83 mmol) of 1,1-di(2-methylcyclopropyl)acetic acid and 1.20g (5.30 mmol) of 5,6-diamino-1,3-dipropyluracil, to obtain 1.20g (yield: 60%) of amorphous 6-amino-5-[1,1-di(2-methylcyclopropyl)]acetyl-amino-1,3-dipropyluracil [Compound (IV): R<sup>1</sup>=R<sup>2</sup>=n-C<sub>3</sub>H<sub>7</sub>;



$X^1=X^2=O$

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 7.58 (brs, 1H), 5.52 (brs, 2H), 4.00 - 3.75 (m, 4H), 2.00 - 0.20 (m, 25H)

885 mg (yield: 78%) of the captioned Compound No. 8 was obtained as a light yellow powder from 1.20g (3.18

mmol) of the thus obtained compound in the substantially same manner as in Example 7.

Melting point: 67.2 - 70.3°C

MS (m/e): 358 (M<sup>+</sup>), 303, 287

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1700, 1655 (shoulder), 1650, 1498

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 12.65 - 12.30 (brm, 1H), 4.11 (t, 2H), 3.99 (t, 2H), 2.20 - 0.20 (m, 25H)

HPLC [AM-312(YMC 150 x 5 $\phi$ ), 50% acetonitrile-water, UV 271 nm, 2.0 mL/min]:

Retention time (relative area): 16.9 min.(19), 17.8 min.(30), 19.7 min.(21), 20.5 min.(30)

#### Example 9

#### 8-(1,1-Dicyclopropylmethyl)-1,3-dipropyl-2-thioxanthine (Compound No. 9)

The substantially same procedure as in Example 1 was repeated using 1.27g (9.09 mmol) of 1,1-dicyclopropylacetic acid and 2.00g (8.26 mmol) of 5,6-diamino-1,3-dipropyl-2-thiouracil [J. Med. Chem., **32**, 1873 (1989)] to obtain 2.42g (yield: 81%) of amorphous 6-amino-5-(1,1-dicyclopropyl) acetylamino-1,3-dipropyl-2-thiouracil [Compound (IV);

$R^1=R^2=n\text{-C}_3\text{H}_7$ ;  $R^4=R^5 = \text{---} \triangle \text{---}$ ;  $X^1=S$ ;  $X^2=O$ ]

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 7.75 (brs, 1H), 5.70 (brs, 2H), 4.60 - 4.20 (m, 4H), 2.05 - 0.20 (m, 21H)

Then, the substantially same procedure as in Example 1 was repeated using 2.00g (5.49 mmol) of the thus obtained compound, and recrystallization was carried out from ethanol-water to afford 1.09g (yield: 57%) of the captioned Compound No. 9 as a white needle crystal.

Melting point: 153.8 - 156.4°C

Elemental analysis (C <sub>18</sub> H <sub>26</sub> N <sub>4</sub> OS)			
Calculated (%):	C 62.40,	H 7.56,	N 16.17
Found (%):	C 62.71,	H 7.94,	N 16.24

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1674, 1493, 1408

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 12.79 (brs, 1H), 4.69 (t, 2H), 4.57 (t, 2H), 2.00 - 1.70 (m, 5H), 1.50 - 1.35 (m, 2H), 1.10 - 0.95 (m, 6H), 0.80 - 0.60 (m, 2H), 0.50 - 0.20 (m, 6H)

#### Example 10

#### 8-(1,1-Dicyclopropylmethyl)-3-propylxanthine (Compound No. 10)

The substantially same procedure as in Example 1 was repeated using 1.68g (12.0 mmol) of 1,1-dicyclopropylacetic acid and 2.00g (10.9 mmol) of 5,6-diamino-3-propyluracil to afford 1.07g (yield: 51%) of 6-amino-5-(1,1-dicyclopropyl) acetylamino-3-propyluracil [Compound (IV):  $R^1=H$ ;  $R^2=n\text{-C}_3\text{H}_7$ ;  $R^4=R^5 = \text{---} \triangle \text{---}$ ;  $X^1=X^2=O$ ] as a pale yellow powder.

NMR (DMSO-d<sub>6</sub>; 90 MHz)  $\delta$  (ppm): 10.55 (brs, 1H), 8.16 (brs, 1H), 6.05 (brs, 2H), 3.73 (t, 2H), 1.80 - 0.10 (m, 16H)

To 2.00g (6.54 mmol) of the thus obtained compound were added to 40 mL of an aqueous 2N sodium hydroxide and 20 mL of dioxane. The mixture was refluxed under heating for two hours, cooled and neutralized. The neutral mixture was extracted three times with a 9:1 mixture of chloroform and methanol, and washed with brine. The mixture was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 2% methanol/chloroform), and recrystallized from ethanol to afford 859 mg (yield: 45%) of the captioned Compound No. 10 as a white crystal.

Melting point: 271.8 - 277.8°C

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1694, 1660, 1499

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NMR (DMSO- $d_6$ ; 90 MHz)  $\delta$  (ppm): 13.03 (brs, 1H), 10.92 (brs, 1H), 3.85 (t, 2H), 1.90 - 0.05 (m, 16H)  
MS (m/e): 288 (M<sup>+</sup>)

## Example 11

### 8-(1,1-Dicyclopropylmethyl)-1,3-dipropyl-7-methylxanthine (Compound No. 11)

To a solution of 2.00g (6.05 mmol) of Compound No. 1 obtained in Example 1 in 60 ml of dimethylformamide were added 2.09g (15.1 mmol) of potassium carbonate and 0.75 ml (12.1 mmol) of methyl iodide. The mixture was stirred at 50°C for one hour and cooled. Insoluble matters were filtered off, and the residue was concentrated under reduced pressure and 200 ml of water was added thereto. The aqueous solution was extracted three times with chloroform and the extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: 20% ethyl acetate/hexane), and recrystallized from heptane to obtain 1.71g (yield: 82%) of the captioned compound No. 11 as a white powder.

Melting point: 69.5 - 70.3°C

Elemental analysis (C <sub>19</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub> )			
Calculated (%):	C 66.25,	H 8.19,	N 16.27
Found (%):	C 66.00,	H 8.55,	N 16.49

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1696, 1660, 1541, 1457

NMR (CDCl<sub>3</sub>; 270 MHz)  $\delta$  (ppm): 4.08 (t, 2H), 3.96 (t, 2H), 3.90 (s, 3H), 1.90 - 1.60 (m, 5H), 1.40 - 1.28 (m, 2H), 1.05 - 0.90 (m, 6H), 0.70 - 0.60 (m, 2H), 0.50 - 0.40 (m, 2H), 0.30 - 0.15 (m, 4H)

## Example 12

### 8-(1,1-Dicyclopropylmethyl)-3-propyl-6-thioxanthine (Compound No. 12)

4.00g (13.9 mmol) of Compound No. 10 obtained in Example 10 was refluxed together with 5.03g (22.6 mmol) of phosphorus pentasulfide in 80 ml of pyridine for 3 hours, and cooled. The reaction mixture was poured into 250 ml of ice water. The precipitates were separated by filtration. The filtrate was concentrated until the volume is reduced to one-fourth. The precipitate was separated by filtration, and suspended in 80 ml of an aqueous 2N sodium hydroxide and an insoluble matter was filtered off. The filtrate was neutralized, and the precipitated crystal was recrystallized from ethanol-water to afford 3.52g (yield: 83%) of the captioned compound No. 12 as a pale yellow needle crystal.

Melting point: 219.4 - 219.8°C

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1661, 1606, 1570, 1505

NMR (DMSO- $d_6$ ; 90 MHz)  $\delta$  (ppm): 12.9 (brs, 1H), 12.1 (brs, 1H), 3.90 (t, 2H), 1.90 - 0.01 (m, 16H) MS (m/e): 304 (M<sup>+</sup>)

## Example 13

### 7-Ethyl-8-(1,1-dicyclopropylmethyl)-1,3-dipropylxanthine (Compound No. 13)

The substantially same procedure as in Example 11 was repeated using 2.00g (6.5 mmol) of 8-(1,1-dicyclopropylmethyl)-1,3-dipropylxanthine obtained in Example 1 and 0.97 ml of ethyl iodide (12.1 mmol) to afford 1.53 g (yield: 71%) of the captioned Compound No. 13 as a pale yellow solid.

Melting point: 80.4 - 82.7°C

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1700, 1659, 1659, 1539, 1417 NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 4.22 (g, 2H, J=7Hz), 4.15 - 3.80 (m, 4H), 1.40 (t, 3H, J=7Hz), 2.00 - 0.20 (m, 21H).

MS (m/e): 358 (M<sup>+</sup>)

## Example 14

## 8-(1,1-Dicyclopropylmethyl)-1,3-dipropyl-7-propylxanthine (Compound No. 14)

The substantially same procedure as in Example 11 was repeated using 2.00 g (6.05 mmol) of 8-(1,1-dicyclopropylmethyl)-1,3-dipropylxanthine obtained in Example 1 and 1.18 ml of propyl iodide (12.1 mmol), and recrystallization was carried out from ethanol-water to afford 1.85 g (yield: 82%) of the captioned Compound No. 14 as a white crystal.

Melting point: 93.2 - 99.6°C

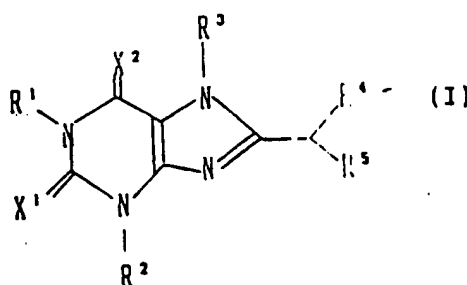
IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1702, 1660, 1541, 1416

NMR (CDCl<sub>3</sub>; 90 MHz)  $\delta$  (ppm): 4.25-3.75 (m, 6H), 2.00-0.20 (m, 26H)

MS (m/e): 372 (M<sup>+</sup>)

## Claims

1. A xanthine compound represented by the following formula I



wherein each of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> independently represents hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; each of R<sup>4</sup> and R<sup>5</sup> independently represents C<sub>3</sub>-C<sub>8</sub> alicyclic alkyl which is optionally substituted with 1 to 3 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, amino and nitro, or substituted or unsubstituted phenyl or naphthyl which is optionally substituted with 1 to 3 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, amino and nitro; and each of X<sup>1</sup> and X<sup>2</sup> independently represents oxygen or sulfur, or its pharmaceutically acceptable salt.

2. The compound according to Claim 1, wherein each of R<sup>4</sup> and R<sup>5</sup> is independently selected from the group consisting of cyclopropyl, 2-methylcyclopropyl, cyclopentyl, cyclohexyl and phenyl.

3. The compound according to Claim 2, wherein both R<sup>1</sup> and R<sup>2</sup> are n-propyl and R<sup>3</sup> is hydrogen or methyl.

4. The compound according to Claim 1, which is selected from the group consisting of 8-(1,1-dicyclopropylmethyl)-1,3-dipropylxanthine, 8-(1-cyclopropyl-1-phenylmethyl)-1,3-dipropylxanthine, 8-[1,1-di(2-methylcyclopropyl)methyl]-1,3-dipropylxanthine and 8-(1,1-dicyclopropylmethyl)-1,3-dipropyl-7-methylxanthine.

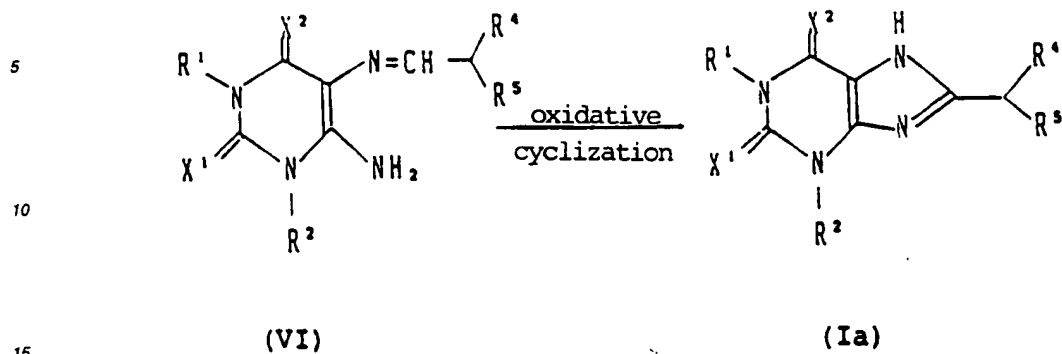
5. A pharmaceutical composition comprising a pharmaceutical carrier and, as an active ingredient, an effective amount of a xanthine compound as defined in Claim 1 or a pharmaceutically acceptable salt thereof.

6. A xanthine compound as defined in Claim 1 for use as a pharmaceutically active agent.

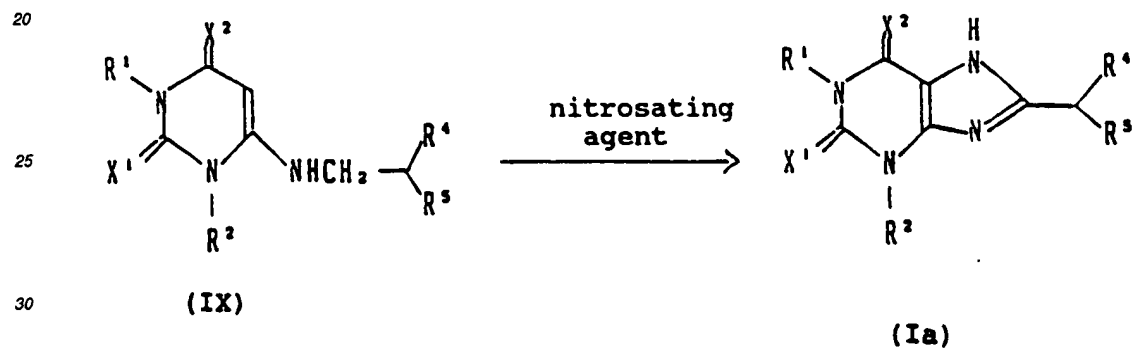
7. A xanthine compound as defined in Claim 1 for use as a diuretic agent, a renal-protecting agent or an antihypertensive agent.

8. A method for the preparation of a xanthine compound of formula (I) as defined in any one of Claims 1 to 4, comprising one of the following reaction schemes:

a) for a compound (Ia) which is a compound of formula (I) wherein R<sup>3</sup> is hydrogen:

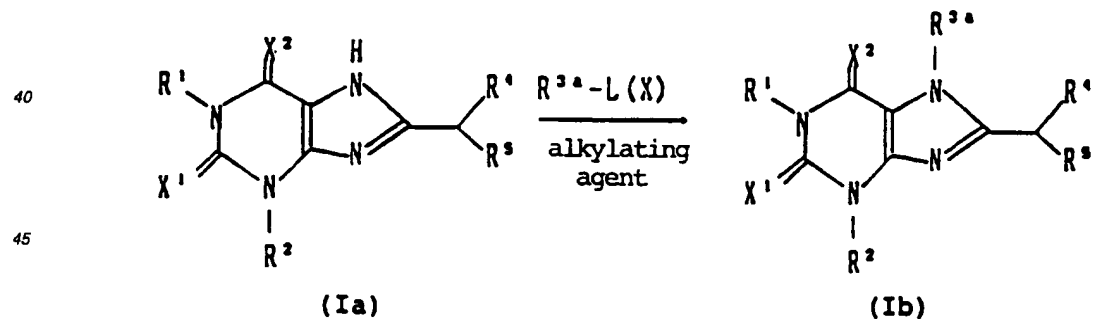


or



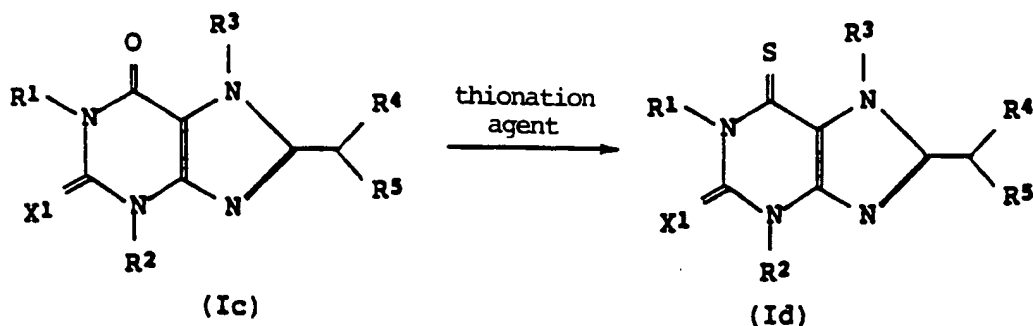
wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, X<sup>1</sup> and X<sup>2</sup> are as defined in Claim 1;

b) for a compound (Ib) which is a compound of formula (I) wherein R<sup>3</sup> is a lower alkyl:



wherein R<sup>3a</sup> represents a lower alkyl and L represents a leaving group and the remaining substituents are as defined in Claim 1;

c) for a compound (Id) which is a compound of formula (I) wherein X<sup>2</sup> is sulfur:

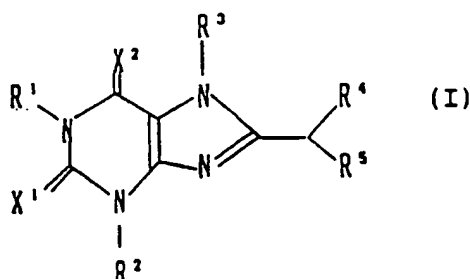


wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and X<sup>1</sup> are as defined in Claim 1.

9. A method for the preparation of a pharmaceutical composition comprising combining a compound as defined in any one of Claims 1 to 4 with a pharmaceutically acceptable carrier.

# Patentansprüche

1. Xanthinverbindung der folgenden Formel I



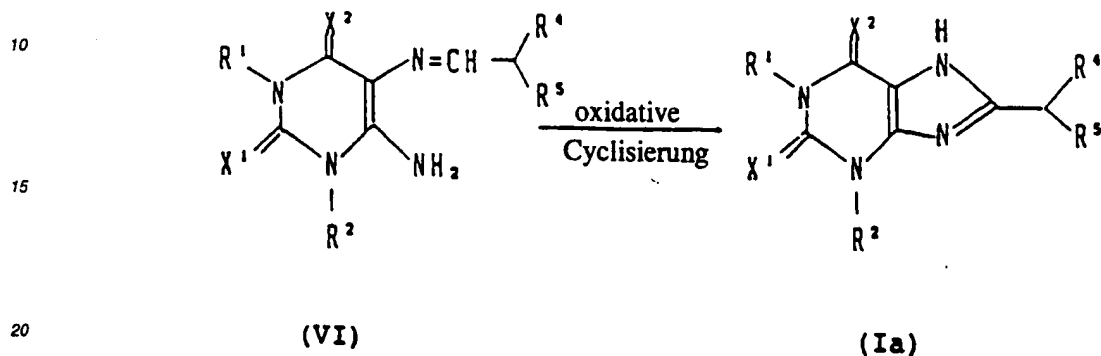
in der jeder der Reste R<sup>1</sup>, R<sup>2</sup> und R<sup>3</sup> unabhängig ein Wasserstoffatom oder einen C<sub>1</sub>-C<sub>6</sub>-Alkylrest darstellt, jeder der Reste R<sup>4</sup> und R<sup>5</sup> unabhängig einen alicyclischen C<sub>3</sub>-C<sub>6</sub>-Alkylrest, der gegebenenfalls mit 1 bis 3 Substituenten, unabhängig ausgewählt aus C<sub>1</sub>-C<sub>6</sub>-Alkyl-, Hydroxyl-, C<sub>1</sub>-C<sub>6</sub>-Alkoxy-, Halogen-, Amino- und Nitrogruppen, substituiert ist, oder eine substituierte oder unsubstituierte Phenyl- oder Naphthylgruppe darstellt, die gegebenenfalls mit 1 bis 3 Substituenten, unabhängig ausgewählt aus C<sub>1</sub>-C<sub>6</sub>-Alkyl-, Hydroxyl-, C<sub>1</sub>-C<sub>6</sub>-Alkoxy-, Halogen-, Amino- und Nitrogruppen, substituiert ist, und jeder der Reste X<sup>1</sup> und X<sup>2</sup> unabhängig ein Sauerstoff- oder Schwefelatom darstellt oder ihr pharmazeutisch verträgliches Salz.

2. Verbindung nach Anspruch 1, in der jeder der Reste R<sup>4</sup> und R<sup>5</sup> unabhängig ausgewählt ist aus Cyclopropyl-, 2-Methylcyclopropyl-, Cyclopentyl-, Cyclohexyl- und Phenylgruppen.
3. Verbindung nach Anspruch 2, in der sowohl R<sup>1</sup> als auch R<sup>2</sup> n-Propylgruppen sind und R<sup>3</sup> ein Wasserstoffatom oder eine Methylgruppe ist.
4. Verbindung nach Anspruch 1, ausgewählt aus 8-(1,1-Dicyclopropylmethyl)-1,3-dipropylxanthin, 8-(1-Cyclopropyl-1-phenylmethyl)-1,3-dipropylxanthin, 8-[1,1-Di(2-methylcyclopropyl)methyl]-1,3-dipropylxanthin und 8-(1,1-Dicyclopropylmethyl)-1,3-dipropyl-7-methylxanthin.
5. Arzneimittel, umfassend einen pharmazeutischen Träger und als Wirkstoff eine wirksame Menge einer Xanthinverbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon.
6. Xanthinverbindung nach Anspruch 1 zur Verwendung als pharmazeutischen Wirkstoff.

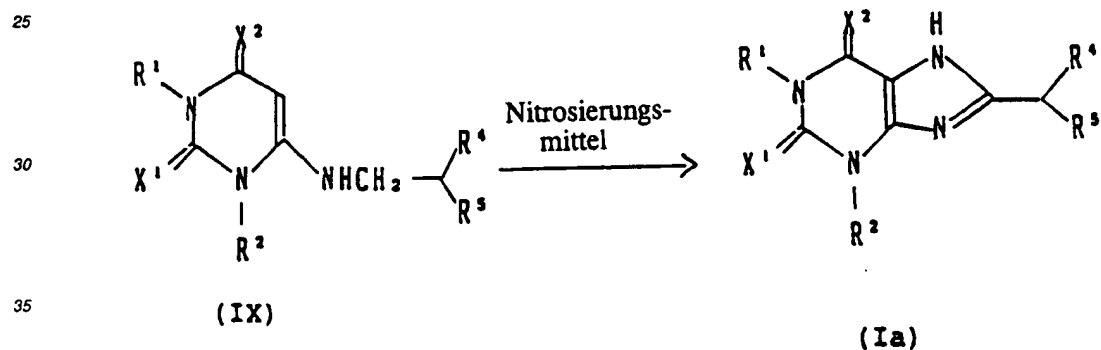
7. Xanthinverbindung nach Anspruch 1 zur Verwendung als Diuretikum, Nierenschutzmittel oder Mittel gegen Bluthochdruck.

8. Verfahren zur Herstellung einer Xanthinverbindung der Formel (I) nach einem der Ansprüche 1 bis 4, umfassend eines der folgenden Reaktionsschemata:

a) für eine Verbindung (Ia), die eine Verbindung der Formel (I) ist, in der R<sup>3</sup> ein Wasserstoffatom ist:

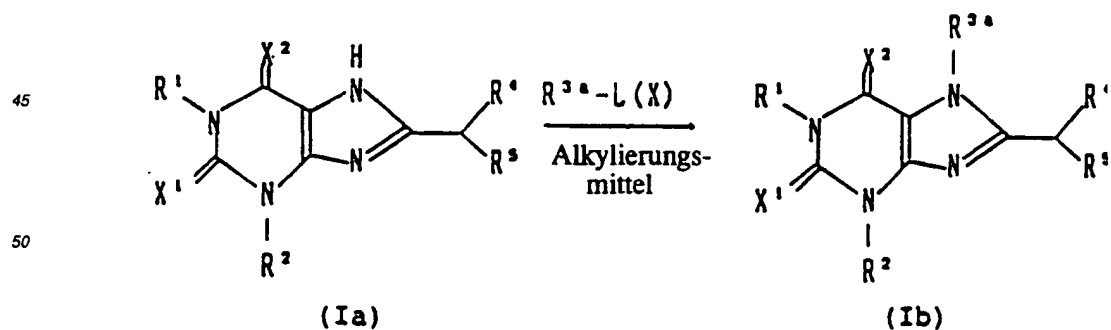


oder



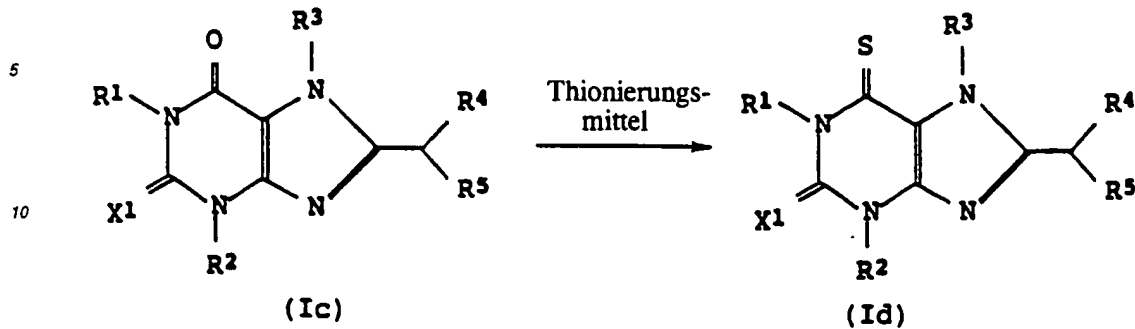
wobei R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, X<sup>1</sup> und X<sup>2</sup> die in Anspruch 1 angegebene Bedeutung haben;

b) für eine Verbindung (Ib), die eine Verbindung der Formel (I) ist, in der R<sup>3</sup> ein Niederalkylrest ist:



wobei R<sup>3a</sup> einen Niederalkylrest darstellt und L eine Abgangsgruppe darstellt und die restlichen Substituenten die in Anspruch 1 angegebene Bedeutung haben;

c) für eine Verbindung (Id), die eine Verbindung der Formel (I) ist, in der X<sup>2</sup> ein Schwefelatom ist:

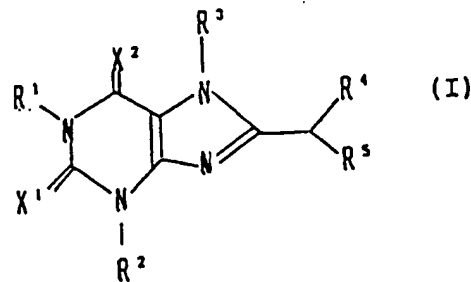


wobei R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> und X<sup>1</sup> die in Anspruch 1 angegebene Bedeutung haben.

9. Verfahren zur Herstellung eines Arzneimittels, umfassend das Zusammenbringen einer Verbindung nach einem der Ansprüche 1 bis 4 mit einem pharmazeutisch verträglichen Träger.

# Revendications

1. Composé de type xanthine représenté par la formule I suivante



dans laquelle R<sup>1</sup>, R<sup>2</sup> et R<sup>3</sup> représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C<sub>1-6</sub>, R<sup>4</sup> et R<sup>5</sup> représentent indépendamment chacun un groupe alkyle alicyclique en C<sub>3-8</sub> pouvant être substitué par 1 à 3 substituants choisis indépendamment dans le groupe formé des résidus alkyle en C<sub>1-6</sub>, hydroxy, alcoxy en C<sub>1-6</sub>, halogéno, amino et nitro, ou un groupe phényle ou naphthyle non substitués ou portant de 1 à 3 substituants choisis indépendamment dans le groupe formé par les résidus alkyle en C<sub>1-6</sub>, hydroxy, alcoxy en C<sub>1-6</sub>, halogéno, amino et nitro, et X<sup>1</sup> et X<sup>2</sup> représentent chacun indépendamment un atome d'oxygène ou de soufre, ou un sel pharmaceutiquement acceptable d'un tel composé.

2. Composé conforme à la revendication 1 dans lequel R<sup>4</sup> et R<sup>5</sup> sont choisis chacun indépendamment dans le groupe formé par les résidus cyclopropyle, 2-méthylcyclopropyle, cyclopentyle, cyclohexyle et phényle.
3. Composé conforme à la revendication 2 dans lequel R<sup>1</sup> et R<sup>2</sup> représentent tous les deux un groupe n-propyle et R<sup>3</sup> un atome d'hydrogène ou un groupe méthyle.
4. Composé conforme à la revendication 1 choisi dans le groupe formé par la 8-(1,1-dicyclopropylméthyl)-1,3-dipropylxanthine, la 8-(1-cyclopropyl-1-phénylméthyl)-1,3-dipropylxanthine, la 8-[1,1-di(2-méthylcyclopropyl)méthyl]-1,3-dipropylxanthine et la 8-(1,1-dicyclopropylméthyl)-1,3-dipropyl-7-méthylxanthine.
5. Composition pharmaceutique contenant un véhicule pharmaceutique et, en tant que principe actif, une quantité efficace d'un composé de type xanthine défini dans la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé.



6. Composé de type xanthine conforme à la revendication 1 pour l'utilisation en tant que principe actif pharmaceutique.

7. Composé de type xanthine conforme à la revendication 1 pour l'utilisation en tant qu'agent diurétique, agent protecteur du système rénal ou agent anti-hypertenseur.

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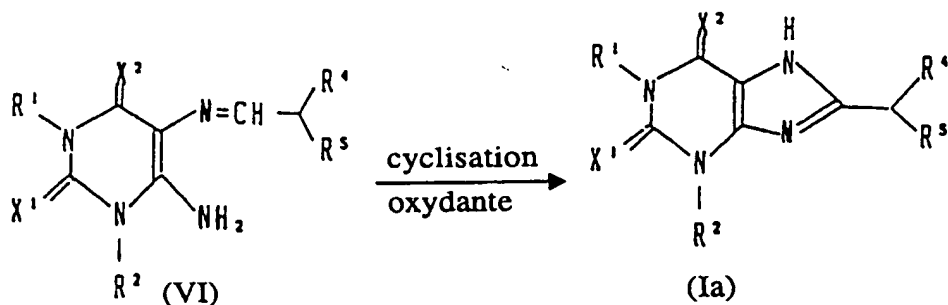
8. Procédé de préparation d'un composé de type xanthine de formule (I) défini dans une quelconque des revendications 1 à 4 consistant en un des schémas réactionnels suivants :

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a) dans le cas d'un composé (Ia) qui est un composé de formule (I) dans lequel R<sup>3</sup> représente un atome d'hydrogène :

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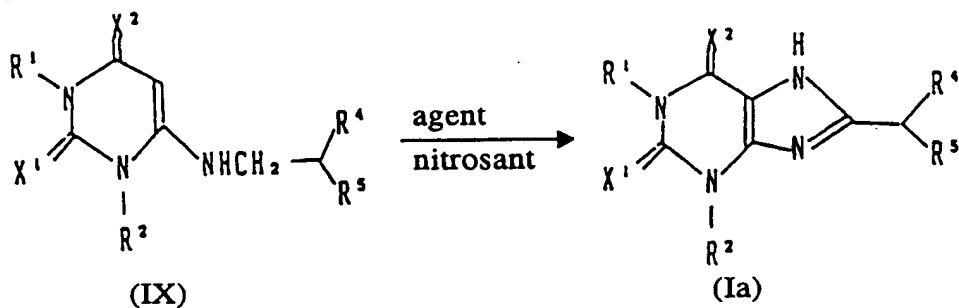


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ou

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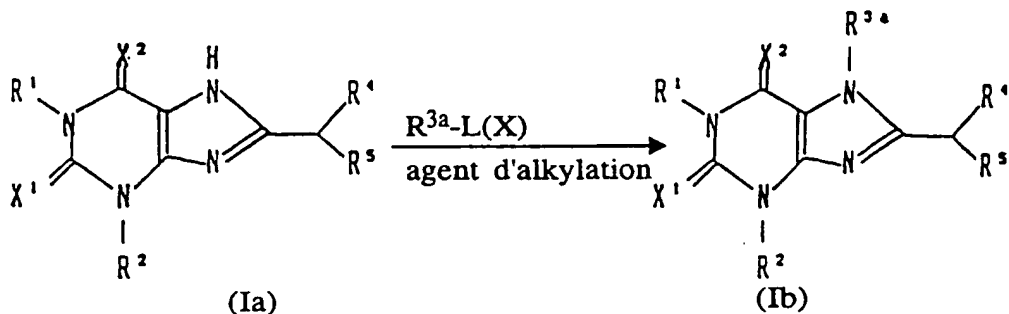
où R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, X<sup>1</sup> et Y<sup>2</sup> sont définis dans la revendication 1 ;

b) dans le cas d'un composé (Ib) qui est un composé de formule (I) dans lequel R<sup>3</sup> représente un groupe alkyle inférieur :

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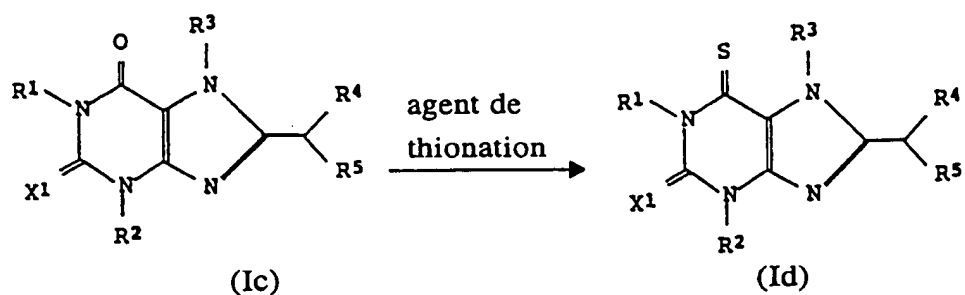
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où R<sup>3a</sup> représente un groupe alkyle inférieur et L représente un groupe partant et les substituants restants sont définis dans la revendication 1 ;

c) dans le cas d'un composé (Id) qui est un composé de formule (I) dans lequel X<sup>2</sup> est un atome de soufre :



où R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> et X<sup>1</sup> sont définis dans la revendication 1.

9. Procédé de préparation d'une composition pharmaceutique consistant à combiner un composé défini dans une  
quelconque des revendications 1 à 4 avec un véhicule pharmaceutiquement acceptable.